PhD thesis
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Childhood adversity in people with first-episode psychosis
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Title: Childhood adversity in people with first-episode psychosis

Subject description: First-episode psychosis, childhood adversity, functioning and metacognition

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Submitted: September 1st 2015

Dedicated to: Ulrik Helt Haahr
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**Abbreviations**

ANOVA Analysis of variance  
CECA.Q Childhood Experience of Care and Abuse Questionnaire  
CTQ Childhood Trauma Questionnaire  
DSM Diagnostic and Statistical Manual of Mental Disorders  
DTD Developmental Trauma Disorder  
DUP Duration of Untreated Psychosis  
FEP First-episode psychosis  
GAF Global Assessment of Functioning scale  
HPA-axis Hypothalamic-Pituitary-Adrenal-axis  
ICD International Classification of Diseases  
IPI Indiana Psychiatric Illness interview  
LQLI Lehman Quality Life Interview  
MANOVA Multivariate analysis of variance  
MAS-A Metacognition Assessment Scale-Abbreviated  
MINI Mini-International Neuropsychiatric Interview  
SE Somatic Experiencing  
PANSS Positive And Negative Syndrome Scale  
PAS Premorbid Adjustment Scale  
PTSD Post-Traumatic Stress Disorder

**Setting and acknowledgements**

This study was performed at the Early Psychosis Intervention Centre in Roskilde, Region Zealand. It was part of a project comparing single family intervention to multiple family intervention within the OPUS treatment, whose research group comprised Erik Simonsen (PI) and Ulrik Helt Haahr (PI), Marlene Buch Pedersen, Hanne-Grethe Lyse Nielsen, Jens Einar Jansen, Christopher Høier Trier and Mette Sjøstrøm Petersen, Ulf Søgaard and Signe Dunker Svendsen (from September 1st 2014). I am very grateful for having been part of this work and for the opportunity to create this PhD study. I especially wish to thank academic advisor Professor Erik Simonsen and clinical advisor Ass. Research Professor Ulrik Haahr therefor. Ulrik Haahr welcomed me as a research year student and provided excellent supervision and guidance in that project, which laid the foundation for the current PhD study. Furthermore, they have provided support, encouragement and inspiration throughout the PhD study and assisted my transformation into a ‘proper’ researcher – not least by
inviting me along on several instructive and entertaining trips! I wish to thank Marlene Buch Pedersen and Hanne-Grethe Lyse Nielsen for providing insights into the OPUS treatment (and Region Zealand) and for welcoming me and my questions and engaging in stimulating discussions. My sincere appreciations to Jens Einar Jansen for always looking at the bright side of ‘life’, for creating decent lounge atmosphere with his DAB radio and of course for being a great sparring partner. I wish to thank Christopher Høier Trier, Mette Sjøstrøm Petersen and Signe Dunker Svendsen for their assistance with data collection and/or management and continually good spirits. It has been a pleasure working with this research group. I also wish to thank secretary Lena Jønsson for her helpful attitude and good spirit, secretary Dorit Mortensen for assisting me in word processing crises and other practical matters and librarian Trine Lacoppidan Kæstel for providing me with books and references and electronic searches.

I am grateful to Dr. Sarah Bendall for welcoming me into the Orygen research environment and the TRIPP group; for the interesting and inspiring discussions we have had and for her supervision, which have increased my understanding of academic writing and the publishing process. I am grateful to Professor Andrew Gumley at the Institute of Health and Wellbeing, Glasgow University for the warm inclusion into both the clinical and research environments, for his continually constructive feedback, for arranging presentations, nights out and not least a personally guided tour through the snow blizzard of the Scottish highlands – I am grateful that the ice axes were just a precaution. From the Institute of Health and Wellbeing, I also wish to thank Dr. White Ross and Kelly Chung for their friendship and always interesting conversations.

I wish to thank my employer Lisbeth Lund Pedersen for her support, not just financially! but also through adamant attendance and engagement at presentations. Furthermore, I am grateful to the assessment committee for their efforts and their readiness to undertake the assignment. I wish to thank my family, not least my in-laws, and my friends for their encouraging moral support throughout this process. Special gratitude is extended to my husband Laust Schouenborg for his continuous support and love for the mediocre.

A final acknowledgement goes to all the participants of this study for their contribution of time and energy and willingness to share their personal stories.
Summary

This study concerns childhood adversity in people with non-affective first-episode psychosis (FEP). There is now evidence that childhood adversities increase the risk of psychosis, but the prevalence of childhood adversity in people with non-affective psychosis remains unclear. Previous studies have found different forms of interpersonal childhood adversities to be central for the risk of non-affective psychosis. Meanwhile, there is accumulating evidence of a dose-response gradient between childhood adversity and non-affective psychosis. This study sought to assess childhood adversity prevalence in a representative sample of people with non-affective FEP and to examine aspects of their relation to the risk of psychosis and to central social and functional factors. The importance of the form and the amount of childhood adversity, i.e. sexual, physical and emotional abuse and physical and emotional neglect, separation and institutionalization, was explored in relation to the risk of psychosis. In addition to risk factors, factors of resilience may influence the development of non-affective psychosis. Perceived support has been found to decrease the risk for PTSD and to affect the risk conveyed by adversities. Perceived support from peers and adults during childhood was hypothesized to diminish the risk of psychosis and ameliorate the risk caused by childhood adversity. Childhood adversity has furthermore been found to be associated with several functional difficulties in different populations. These relations have been sparsely studied in people with non-affective psychosis, though it is likely that childhood adversity may cause some of the functional decline that the majority experience in both premorbid and psychotic phases. Childhood adversities were hypothesized to be associated with worse premorbid social and academic adjustment trajectories; worse global functioning prior to treatment start; and lower current educational, vocational and living functioning. It was hypothesized to be associated with less family contact. The family is one of the primary sources of support for people with FEP and it is therefore important to know if this relation is affected by previous childhood adversity. Studies indicate that metacognitive abilities are a specific part of functioning that seem especially associated with non-affective psychosis, but few studies have compared metacognition in people with FEP to non-clinical control persons. Positive and negative symptoms constitute the core of non-affective psychosis and it remains unclear how metacognition affects both positive and negative symptomatology. To examine these questions, metacognitive abilities were compared to a non-clinical control group and to positive and negative symptom profiles. The latter was done through identification of symptom profiles based on positive and negative symptom levels.
The research questions were examined in a cross-sectional case-control study, which included 101 persons with non-affective FEP and 101 non-clinical control persons matched by gender, age and parental education. The FEP group was included consecutively over a two-year period from April 2011 to April 2013 and the control group from October 2013 to May 2014. The assessment instruments comprised the CTQ, CECA.Q, PANSS, PAS, GAF, Lehman Quality of Life Interview, IPII, MAS-A and the MINI 6.0 for the control group. The childhood adversities thus included sexual, physical and emotional abuse, physical and emotional neglect, separation and institutionalization. Statistical analyses comprised t-tests and Mann-Whitney U-tests, ANOVAs, MANOVAs and logistic regression analyses.

Fifty-two percent of the FEP group and seven percent of the control group had experienced three or more adversities. Regarding the importance of the form of childhood adversity, all forms predicted the risk of psychosis. However, when they were corrected for each other, only emotional abuse, physical and emotional neglect, parental separation and institutionalization remained predictors of psychosis. All the odds ratios from the different forms were reduced considerably by the adjustments and all the adversities were correlated with at least two other forms of adversity.

Concerning a dose-response relation, we found that the risk of psychosis increased with the number of childhood adversities.

Peer and adult support during childhood was less prevalent in the FEP group and peer support continued to reduce the risk of psychosis after adjustment for childhood adversities. Peer but not adult support diminished the risk of psychosis caused by childhood adversities. Regarding current family contact, it was found to be lower for those with more childhood adversities. Childhood adversities were equally common for all the different social and academic premorbid trajectories.

Childhood adversities were negatively correlated with global functioning the year prior to treatment start, while they were unrelated to current educational, vocational and living functioning.

Metacognitive abilities were lower in the FEP group compared to the control group. In the FEP group, they were lower for the two groups with high negative symptom scores, but not for the one group with high positive symptoms and low negative symptom scores. Thus, metacognition was consistently associated with high negative, but not with positive symptom scores.

As numerous studies have found that physical and sexual abuse increase the risk of psychosis, we think that it would be incorrect to conclude that they did not play a role for the risk of psychosis in our FEP sample. Their insignificance was caused by the fact that almost all with sexual or physical abuse had experienced other adversities as well. Thus, this approach falsely diminishes the effects...
of the assessed childhood adversities. Since numerous different studies have found different adversities to be rendered insignificant and since they have found different adversity profiles, it may be that the form of childhood adversity is not crucial for the risk of psychosis. Instead, it may be that shared aspects of traumatization convey the risk of psychosis, such as HPA-axis dysregulation or psychological mechanisms such as feelings of social defeat and dissociation. The data support that the amount, and implicitly the frequency and severity, of childhood adversity is crucial for the risk of non-affective psychosis. Taken together, it may be that a conceptualization that combines the effects of the different forms of childhood adversity may offer a more correct risk estimate. This may prompt research to explore shared mechanisms and to increase awareness of the likelihood of confounding by other adversities when seeking to examine single adversity forms. The findings of lower levels of perceived support from adults and peers during childhood in the FEP group suggest that they may be important resilience factors. This should be further studied in similar research designs and in prospective cohort studies. The data regarding premorbid trajectories and global functioning propose that adversities only affected them when the psychotic breakdown was imminent or happening. This may only be fully examined in longitudinal studies. Theoretically, metacognition is considered closely linked to childhood adversity, and since this study is the first to explore the association with adequate adversity assessment, replication of this finding is required. Metacognitive abilities were lower in the FEP group, which supports their importance and future investigation. Our findings suggested that the level of negative, but not positive symptoms is affected by metacognition. Previous findings of relations with positive symptoms may have been confounded by negative symptoms, and it is important that future researchers are aware of this.

Overall, the high prevalence of childhood adversity and the finding that peer support ameliorated the risk of psychosis conveyed by childhood adversities, suggests that preventive strategies for vulnerable children should be instigated. It furthermore proposes that current interventions should implement thorough childhood adversity assessment and approaches that deal with childhood adversity. This is supported by the finding of an association between more childhood adversities and less current family contact, as family relations may be improved by interventions that deal with childhood adversity. Additionally, individuals with past adversity exposure may require more assistance in attaining and maintaining social support. The high prevalence of childhood adversity and poor metacognitive abilities supports the importance of providing psychotherapy for people with non-affective psychosis, as both the consequences of childhood adversity and metacognitive abilities are responsive to such intervention. Additionally, the strong association between
metacognition and negative symptoms may suggest that improvements of metacognition can reduce the level of negative symptoms, which is one of the greatest challenges of current psychosis interventions. Future research should explore this hypothesis.

**Dansk resumé (Danish summary)**

Dette studie omhandler barndomstraumer hos personer med non-affektiv debuterende psykose (FEP). Det er påvist at barndomstraumer øger risikoen for psykose, men det er stadig uvist hvor stor forekomsten af barndomstraumer er hos personer med FEP. Tidligere studier har vist at forskellige typer af interpersonelle barndomstraumer er essentielle for risikoen for non-affektive psykoser. Der er samtidig stigende evidens for at risikoen for psykose stiger med øget antal af barndomstraumer.


Syvogfirs procent af FEP gruppen og 37% af kontrolgruppen havde været udsat for minimum et alvorligt barndomstraume. Mht. vigtigheden af typen af traumer, så øgede alle typerne risikoen for psykose, men da de blev statistisk korrigeret for hinanden forblev kun følelsesmæssigt overgreb, fysisk og følelsesmæssig omsorgssvigt, separation og institutionalisering at være signifikante risikofaktorer for psykose. Alle odds ratioer fra de forskellige typer reduceredes betydeligt ved korrektionen og alle traumerne var korrelerede til mindst to andre typer af trauma. Med hensyn til mængden af traumer så fandt vi at 52% af FEP gruppen og 7% af kontrol gruppen havde været udsat for tre eller flere barndomstraumer og at risikoen for psykose steg med stigende antal barndomstraumer. FEP gruppen rapporterede at have oplevet mindre støtte fra jævnaldrende og voksne gennem barndommen end kontrolgruppen, og støtte fra jævnaldrende reducerede risikoen for psykose også efter at der var korrigeret for barndomstraumer. Oplevet støtte fra jævnaldrende men ikke fra voksne nedsatte den risiko for psykose der var bevirket af barndomstraumer. Med hensyn til familiekontakt så fandt vi at de med flere barndomstraumer så familien sjældnere. Barndomstraumer var lige hyppige for de forskellige præmorbide sociale og akademiske tilpasningsforløb. Barndomstraumer var negativt korreleret med almen funktion året før behandlingsstart, men de var ikke relateret til opnået uddannelse, beskæftigelse og boligmæssig funktion. FEP gruppen havde dårligere metakognitive evner end kontrolgruppen. I FEP gruppen, var de metakognitive evner lavere for de to grupper med høje negative symptom scores, men ikke for gruppen med høje positive og lave negative symptom scores. Med andre ord så var metakognition konsekvent associeret med negative men ikke med positive symptomer. Da mange forskellige studier har fundet at fysiske og seksuelle overgreb øger risikoen for psykose, så virker det usandsynligt at de ikke spillede en rolle for udviklingen af psykose i vores FEP gruppe. I stedet fandt vi at deres non-signifikans skyldtes at næsten alle med seksuelle eller fysiske overgreb
også havde været udsat for andre barndomstraumer. Denne fremgangsmåde mindsker altså effekten af de rapporterede barndomstraumer. Forskellige studier finder at forskellige typer af barndomstraumer er essentielle og at forskellige FEP grupper har forskellige profiler af barndomstraumer. Dette kunne skyldes at typen af barndomstraumer ikke er essentiel for risikoen for psykose, men at det i stedet er fælles aspekter ved traumatiseringen der bærer risikoen for psykose, såsom HPA-axis dys-regulering eller psykologiske mekanismer såsom dissociation eller følelser af socialt nederlag. Vores data understøtter at mænd, og indirekte frekvensen og alvorsgraden, af barndomstraumer er essentielt for risikoen for non-affektiv psykose.

Samlet set er det muligt, at en konceptualisering der kombinerer effekterne af de forskellige typer af barndomstraumer vil give en mere korrekt risikoestimering. Disse overvejelser kan muligvis øge opmærksomheden omkring fælles mekanismer og om risikoen for confounding af andre barndomstraumer ved undersøgelsen af enkelte typer. De lave niveauer af oplevet støtte fra jævnaldrende og voksne gennem barndommen implicerer at de kan være vigtige resiliens faktorer. Dette burde undersøges yderligere både i lignende studier og i prospektive kohorte studier. Fundene vedrørende de præmorbide tilpasningsforløb og det almindelige funktionsniveau tyder på at barndomstraumer kun påvirker funktionsniveauet når det psykotiske sammenbrud er nær forestående eller i gang. Dette kan muligvis kun blive ordentligt undersøgt i prospektive studier. Teoretisk set er metakognition meget tæt forbundet til barndomstraumer, og eftersom dette studie er det første der undersøger dette forhold med tilstrækkelig traume assessment, er det nødvendigt at repetere disse fund. At de metakognitive evner var lavere i FEP gruppen sammenlignet med kontrolgruppen støtter deres betydning for non-affektiv psykose. Derudover viser vores fund at metakognition påvirker niveauet af negative, men ikke positive symptomer. Tidligere fund af associationer med positive symptomer har muligvis været confoundet af negative symptomer, hvilket fremtidige studier bør tage højde for.

Alt i alt viser den øgede risiko for psykose fra barndomstraumer og mangel på oplevet støtte at der bør iværksættes præventive strategier for udsatte børn. De viser ydermere at nuværende interventioner bør udføre en grundig assessment af barndomstraumer og forholde sig til hvordan de kan behandles. Det samme viser fundet af associationen mellem barndomstraumer og mindre familiekontakt da det er muligt at familierelationerne kan forbedres hvis der bliver taget hånd om tidligere traumer. Derudover kan det være at personer der har været udsat for barndomstraumer har brug for mere assistance til at opnå og vedligeholde social støtte. Den høje prævalens af barndomstraumer og dårlige metakognitive evner støtter endvidere vigtigheden af at der bliver
tilbudt psykoterapi, da både følgevirkninger af barndomstraumer og metakognitive evner responderer godt herpå. Ydermere er det muligt er den stærke association mellem metakognition og negative symptomer kan betyde at metakognitiv bedring kan reducere niveauet af negative symptomer, hvilket er en af de største udfordringer for nuværende interventioner. Fremtidige studier bør undersøge denne hypotese.
Aims and hypotheses

i. To examine the prevalence of childhood adversity in people with non-affective FEP and a matched non-clinical control group.

ii. To examine the importance of the type and number of childhood adversities for the risk of psychosis.

iii. Childhood adversities will negatively affect premorbid trajectories, years of education and global, occupational and living functioning.

iv. To examine whether perceived support during childhood decreases the risk of psychosis and whether perceived support and family contact is associated with childhood adversity.

v. The FEP group will have lower metacognitive abilities than the non-clinical control group.

vi. Metacognitive abilities will be negatively associated with number of childhood adversities.

vii. Poorer metacognitive abilities and more childhood adversities will be associated with higher levels of positive and negative symptoms independently and together.

Background

The risk developmental model

More than 100 years of research into non-affective psychosis has failed to produce a precise definition or aetiological model (Isohanni et al., 2005; Tandon, 2012; Tandon et al., 2008; Tandon and Maj, 2008). Instead it has become apparent that no single factor or model can explain non-affective psychoses (or other psychiatric diagnoses) and that aetiopathogenic models must include both genetic and environmental factors (Guidotti et al., 2014; Kendler, 2005). An understanding of the causality and symptoms of disorders must be based on knowledge about risk factors. Risk factors provide the basis for the aetiopathogenic models, which influence preventive strategies and interventions, and the explanations given to service users, their relatives and the general population.

A risk factor is defined as “any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury” (“WHO | Risk factors,” n.d.). A current neurodevelopmental risk factor model for non-affective psychosis would thus include all the
identified risk factors, which occur from before birth and up until the full-blown psychosis. These are pre- and perinatal conditions and complications, such as genetic risk factors (International Schizophrenia Consortium, 2008; Kim et al., 2015; Lichtenstein et al., 2009; Stefansson et al., 2008; Walsh et al., 2008), paternal age (Matheson et al., 2011) and pre-natal infections, obstetric complications (Meyer and Feldon, 2009; Schmitt et al., 2014) and lifespan environmental risk factors, such as childhood adversity (Filippo Varese et al., 2012), ethnic minority status (Bourque et al., 2012; Matheson et al., 2011), urban living (Matheson et al., 2011; Vassos et al., 2012), cannabis use (Henquet et al., 2005; Matheson et al., 2011) and life events just prior to psychosis onset (Bebbington et al., 1993). Less firmly established risk factors include fewer years of parental education, lower paternal occupational status, poorer residential area and bigger income inequality (Kirkbride et al., 2014; Werner et al., 2007). A suggestion for such a neurodevelopmental risk factor model has been presented in figure 1.

Figure 1. A neurodevelopmental risk factor model.

In psychiatry, risk factors are mainly identified from cohort, case-control and cross-sectional studies. Cohort studies are the most robust method, as exposure to putative risk factors can be measured before the outcome and thus shown to precede it; they also avoid selection or recall bias and thus provide true incidence rates and measures of relative risk. However, loss at follow-up may introduce bias, especially in relation to long-term outcomes, and the cohort process can be expensive and complicated when one is interested in rare outcomes, such as non-affective psychosis. Case-control studies are less robust due to the risk of selection, recall or observational bias and they can only provide odds ratios, not incidence rates. Odds ratios are considered equivalent to relative risk in the case of rare outcomes, such as non-affective psychosis (Kleinbaum and Klein, 2010, p. 16). Cross-sectional studies are vulnerable to the same biases as case-control studies and are merely hypothesis generating as they estimate associations between exposure and outcome but do not provide estimates of risk.
Current paradigms influence the search for risk factors as they affect the opinions of researchers and funding bodies. Some researchers argue that psychiatry, especially in the field of non-affective psychosis, has been dominated by the biomedical perspective (Cullberg, 2006, pp. 212–226) according to which non-affective psychosis is caused by structural and functional impairments in the brain, often of genetic origin, and can thus be explained in terms of neurobiological processes (Bentall, 2004, pp. 153–157; Kendler, 2005). The dominance of the biomedical perspective is believed to be responsible for the relative increase in research into genetic and biological risk factors rather than psychological ones that psychiatry has witnessed over the past 30 years. This development is illustrated in figure 2.

**Figure 2. The development of research in non-affective psychoses from 1960.**

![PsycINFO search hits of (psychosis AND risk AND...)](image)

Notes: The search strings were (psychosis OR schizophrenia) AND (risk OR cause) AND 1. Genetic, 2. Biological, 3. Psychological.

The lack of research into childhood adversity in people with non-affective psychosis and the failure to acknowledge its relevance has similarly been blamed on the biomedical paradigm. It has been held responsible for the general failure to assess childhood adversity and the tendency to change diagnoses of non-affective psychosis to trauma-related diagnoses when there is evidence of childhood adversity (Read, 1997). Non-affective psychosis was one of the last diagnostic categories to recognize childhood adversity as a possible risk factor. They have since the eighties and nineties been considered risk factors for anxiety and depressive disorders (Bifulco, 1991; Browne, 1986; Nemeroff, 2004), bipolar disorder (Maniglio, 2013), substance abuse disorders (De Bellis, 2002).
and eating and personality disorders (Sansone and Sansone, 2007). This is illustrated in figure 3, which shows that before the 1990s there was almost no research into adversity as a risk factor for psychosis or schizophrenia. The search string included (schizophrenia/psychosis AND risk/cause AND adversity/trauma).

The graph also illustrates the steady growth in this research field since 1990. In 2001 Read et al. put forward a theoretical model – the traumagenic neurodevelopmental model – which suggested that childhood adversity could cause non-affective psychosis (Read et al., 2001) and in 2005 they published a literature review which concluded that childhood adversity could cause psychotic symptoms (Read et al., 2005). These claims were, however, contested by several researchers and competing reviews concluded that the evidence was too sparse (Morgan and Fisher, 2007). More rigorous studies were carried out and in 2012 two meta-analyses concluded that childhood adversity increases the risk of developing non-affective psychosis (Matheson et al., 2012; Filippo Varese et al., 2012). Before reviewing this literature, I will explain what childhood adversity and first-episode psychosis (FEP) entail.

**Conceptualizing childhood adversities**

Since the 1980s, the only official definitions of trauma in psychiatry have been those related to Post-Traumatic Stress Disorder (PTSD) in the diagnostic systems DSM-5 and ICD-10 (American...
DSM-5 defines trauma as “exposure to actual or threatened death, serious injury, or sexual violence” either through direct experience or as witness or through the account of a close other (American Psychiatric Association, 2013). ICD-10 defines trauma as “exposure to a stressful event or situation (either short or long lasting) of exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone” (World Health Organization, 2007). These definitions, which are used in the diagnosis of PTSD, only encompass exceptional, life-threatening situations, with the exception of sexual violence, which was added to DSM-5. The narrowness of the definitions gives rise to concerns in relation to PTSD and to general perceptions of what trauma is. The inclusion of sexual violence in the DSM-5 definition represents an acknowledgment that non-life-threatening experiences can cause PTSD and raises the question of whether other non-life-threatening experiences should also be included. As Van der Kolk has noted, psychological forms of trauma such as emotional abuse and neglect are excluded although they have been associated with PTSD symptoms both in children and in adults (Basile et al., 2004; Higgins and McCabe, 2003; Van der Kolk, 2005). A discussion of the DSM IV definition, which included threat to one’s physical integrity instead of sexual violence, suggested that all the forms of trauma that can cause PTSD should be identified so they could be included in the definition (Weathers and Keane, 2007). These authors also noted that the severity of trauma may be one determinant of whether PTSD follows. The thrust of these suggestions was that trauma should be defined in terms of the response it elicits rather than its objective properties. Combining recognition of the importance of the response with an objective definition of trauma is a constant challenge for those who seek to define and understand it.

Society and the research community really began acknowledging and attending to the consequences of childhood trauma in the second part of the last century (Cicchetti and Valentino, 2006, pp. 132–133), and the last three decades have seen a boom in research into childhood abuse and neglect, which have been shown to have wide-ranging short and long-term consequences (New Directions in Child Abuse and Neglect Research, n.d., p. 1). As well as the above-mentioned difficulty of providing an objective definition of something which is essentially a response phenomenon, it is difficult to arrive at an agreed definition of childhood trauma because such a definition would need to be fit for societal, legal and medical purposes (Cicchetti and Valentino, 2006, pp. 132–133). A degree of consensus has nevertheless been reached in the research community. There is general acknowledgement that certain types of childhood experience are traumatising, on the grounds that
they have been found to cause severe psychological and behavioural problems (Cicchetti and Valentino, 2006, pp. 132–133). Traumatizing childhood experiences include sexual and physical abuse, emotional maltreatment and neglect. Sexual abuse is defined as any sexual contact between an adult and a child and any unwanted sexual contact between two under-age children. Physical abuse is defined as any purposefully imposed physical harm. Emotional maltreatment is defined as persistent failure to meet emotional needs, but is often divided into emotional abuse and emotional neglect. Emotional abuse is the experience of behaviour motivated by hate, and neglect and lack of love. Physical neglect is a lack of basic care and observation (Cicchetti and Valentino, 2006, pp. 132–133).

Several researchers have suggested definitions of childhood trauma for inclusion in diagnostic systems. Complex Trauma was a term that was developed to create a complex PTSD diagnosis because there was evidence that lasting, severe, inescapable trauma had worse consequences than single events (Courtois, 2008; Herman, 1992). It was proposed that Developmental Trauma Disorder (DTD) should be included in DSM V as the childhood equivalent of PTSD since there was no comprehensive trauma diagnosis for traumatized children (Van der Kolk, 2005; van der Kolk et al., 2009). The DTD definition of trauma was based on the concept of Complex Trauma and large population studies. The authors’ intention was to develop criteria for trauma that focused not on the type of trauma, but on its severity, persistence and duration (van der Kolk et al., 2009, pp. 5–6). However, as with PTSD, the objective criteria were designed to match the symptoms of a disorder, and thus trauma was defined as i. witnessing or experiencing interpersonal violence and ii. disruption of caregiving. This excludes all trauma not involving physical violence and thus, like the PTSD definition of trauma, the DTD definition ignores purely psychological trauma.

The prominent trauma clinicians and researchers behind the widespread trauma treatment Somatic Experiencing (SE) define trauma as “an event that causes a long-term dysregulation in the autonomic and core extrapyramidal nervous system” (Levine and Mate, 2010; Payne et al., 2015). Their theory and treatment focus on the involuntary reactions to stress and trauma controlled by subcortical brain areas and are based on clinical work with trauma survivors as well as human and animal research. Animal research has shown that inflicting stress above a certain intensity and duration can cause an otherwise temporary dysfunction to become chronic (Gellhorn, 1967). SE emphasizes the enduring imbalance in the organism – the failure to return to a habitual state (Levine and Frederick, 1997; Payne et al., 2015). It follows from this definition that the psychological and physical responses to trauma have a dimensional quality. The authors also emphasize that the
consequences of trauma depend on the actions available to the individual at the time (Levine and Mate, 2010), which is in line with findings from animal research showing that uncontrollable stress generates more autonomic activity (Foa, Zinbarg, & Rothbaum, 1992). This is important for our understanding of childhood trauma, because a child is dependent upon others. In summary, trauma is any event that causes lasting dysfunction of the nervous system; this implies that its severity, duration, controllability and perceptions are important. This definition provides insight into the probable mechanisms at work in traumatized people and the dynamic nature of trauma.

Objective definitions of childhood have made the retrospective identification and assessment of people who may have been traumatized easier. Sexual and physical abuse have gained most attention in psychosis research whilst emotional abuse, neglect, institutionalization and separation have been relatively overlooked (Bonoldi et al., 2013; Matheson et al., 2012; Read et al., 2005) although this imbalance has been somewhat redressed during the last decade. Use of standardized assessment tools, such as the CTQ and the CECA.Q has increased (Bernstein and Fink, 1993; Bernstein et al., 2003; Bifulco et al., 1994; Smith et al., 2002) and the importance of attachment relationships in the context of non-affective psychosis has been recognised (Berry et al., 2007; Harder, 2014; Read and Gumley, 2008). Institutionalization and loss of, or separation from a primary caregiver have also been included in definitions of childhood adversity. Like emotional neglect they are considered examples of inadequate caregiving (Read and Gumley, 2008) and can be included in the category of attachment trauma. Attachment trauma occurs because of problems in the relationship between a child and its primary caregivers and involves the development of an insecure and/or disorganised attachment between the child and caregiver. It is characteristic of relationships, which involve abuse, neglect or disrupted caregiving (Jon G. Allen, 2012, p. 46).

**Early detection and intervention in FEP**

Non-affective psychosis is a heterogeneous term for highly differing clinical conditions. The diagnosis spans from schizophrenia simplex where only negative symptoms are present to delusional disorders where only delusions occur (American Psychiatric Association, 2013; World Health Organization, 2007). Diagnoses of schizophrenia containing positive symptoms account for the vast majority of non-affective psychoses., while around 60% of those with non-affective FEP experience negative symptoms (Lyne et al., 2012; Üçok and Ergül, 2014) (defined as a rating of ≥ 3 on any item on the Scale for the Assessment of Negative Symptoms (Andreasen, 1983)). In addition to positive and negative symptoms, a diagnosis of non-affective symptoms may comprise cognitive
difficulties, disorganized behaviour, speech and thought disorder. Positive symptoms comprise delusions, hallucinations and negative symptoms comprise apathy, anhedonia, alogia (e.g. poverty of speech) and affective flattening. They are non-affective because they appear independent from depressive and manic disorders, which comprise the affective psychoses, though people with non-affective psychosis often have symptoms of depression (13 - 70%) (Barnes et al., 1989; Birchwood et al., 2000a) and anxiety (30 - 85%) (Pokos and Castle, 2006). Schizophrenia was first systematically described by Kraepelin in the 1890s; Kraepelin named the condition ‘dementia praecox’ on the basis of the intellectual impairments observed (Hoff, 2015; Jablensky, 2007; Kraepelin, 1919). Bleuler built on this work, coming to understand the condition as a disturbance of association and splitting of personality functions and renaming it schizophrenia (Arieti, 1955; Bleuler, 1950; McGlashan, 2011). Kraepelin and Bleuler’s research was the foundation on which schemes to differentiate and categorise non-affective psychoses were based; work which was formalised in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (first edition 1952) and the International Statistical Classification of Diseases and Related Health Problems (ICD) (first edition 1949). These schemes continue to have a major impact on the psychiatric research and clinical communities (Hoff, 2015; Jablensky, 2007; McGlashan, 2011).

FEP is a term encompassing all first episodes of non-affective psychosis, but is most often used to refer to episodes occurring in adolescence and early adulthood (18-35 years of age), the periods when the incidence of non-affective psychosis is highest (Leung and Chue, 2000). FEP has been of special interest since the 1990s, when it was shown that some people with FEP experience a dramatic decline in psycho-social functioning in the early phase of their psychosis, the so-called ‘critical period’1. It was hypothesised that FEP would be especially responsive to treatment during the critical period, and this led to the development of special services whose aim was to improve outcomes through early detection and intervention (Birchwood et al., 1998; Edwards et al., 1994; McGlashan and Johannessen, 1996; McGorry et al., 2008, 1996). Most contemporary early intervention services are out-patient clinics using a case-management model based on frequent meetings, family psycho-education and interventions, group work including social skills training and psycho-education, and individual assistance with social problems and anti-psychotic pharmaceuticals (International Early Psychosis Association Writing Group, 2005). Meetings with

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1 It was later discovered that people can recover much later than the so-called critical period of 2-5 years from onset (International Early Psychosis Association Writing Group, 2005).
the case manager may include individual psychotherapy, but this is not given the same priority as family interventions.

Although modern psychiatric services have improved short- and long-term outcomes (Hegelstad et al., 2012; Henry et al., 2010; Secher et al., 2014), non-affective psychosis remains one of the most disruptive psychiatric disorders. Interventions continue to evolve; recent developments include active vocational assistance (Christensen et al., 2015) and trauma-informed interventions (Bendall, S, 2014). Although people with non-affective psychoses still have worse quality of life (Evensen et al., 2012; Henry et al., 2010), worse social and vocational functioning (Austin et al., 2013; Hegelstad et al., 2012; Henry et al., 2010) and a reduction in life expectancy of about 20 years (Laursen et al., 2014) compared with the general population, the early intervention paradigm has improved the typical course and outcome and led to better understanding of the development and course of psychosis (Hegelstad et al., 2012; Henry et al., 2010). These advances have been especially pronounced in relation to three aspects of FEP, namely the premorbid and prodromal phases and the duration of untreated psychosis (DUP). It is recognized that FEP is often preceded by a prodromal phase of uncharacteristic problems, such as depressive, cognitive and social disturbances. This prodromal phase varies in duration and usually overlaps with the premorbid period, which is considered to extend from birth to six months prior to the occurrence of the first clear symptoms of psychosis. The DUP is the length of the interval between the emergence of clear, positive psychotic symptoms lasting at least one week and the instigation of antipsychotic treatment (Melle et al., 2006). Poor premorbid functioning predicts more negative symptoms, whereas a long DUP predicts more positive and more negative symptoms; both have a detrimental impact on recovery (Austin et al., 2013). Early intervention also has clear benefits from a research perspective: people with FEP are more easily brought to represent a generalizable group as they have not been affected by previous treatments, such as antipsychotic medication, and have better recollection of their childhood.

**Prevalence and risk of childhood adversities in non-affective psychosis**

Several high quality studies of childhood adversity and psychosis have emerged in the last decade. They include large register studies (Cutajar et al., 2010; Elklit and Shevlin, 2011), prospective and cross-sectional population studies (Schreier et al., 2009; Shevlin et al., 2011, 2008; van Nierop et al., 2014b) and case-control studies (Heins et al., 2011; McCabe et al., 2012; Morgan and Fearon, 2007). Previous reviews noted serious methodological weaknesses and were cautious in their
conclusions (Morgan and Fisher, 2007), but more recent meta-analyses have stated that childhood adversity increases the risk of developing non-affective psychosis (Matheson et al., 2012; Filippo Varese et al., 2012).

Varese et al.’s meta-analysis was based on 36 studies of various designs, i.e. case-control studies, register, prospective and cross-sectional population studies. Analysis of studies that did not control for potential confounding variables showed that childhood adversity increased the risk of developing psychosis by a factor of 2.8 (OR 2.8 (2.34–3.31)); analysis of the 12 studies which did control for potential confounders found a 2.7 times increase in risk (OR = 2.72 (2.08–3.68), p < .001). As individual factors sexual, physical or emotional abuse, neglect and bullying all increased risk, with ORs ranging from 2.38 (1.98–2.87) to 3.40 (2.06–5.62) and p-values < .001. Parental death did not appear to increase the risk of developing psychosis. Likewise, Matheson concluded that people with a diagnosis of schizophrenia were 3.6 times more likely to have been exposed to childhood adversity than non-clinical controls (OR 3.6 (2.08–6.23)). A third meta-analysis concluded that the incidence of exposure to various forms of childhood adversity in psychosis populations was as follows: sexual abuse, 26%; physical abuse, 39%; emotional abuse, 34% (Bonoldi et al., 2013).

It is however, as mentioned in the Introduction, preferable to rely on data from FEP populations to establish the prevalence of childhood adversity in people with non-affective psychosis. As part of the planning of the project reported here a systematic search for FEP studies was carried out in the electronic databases Medline, PsycInfo and Embase (April 2012). The search strings are reported in Appendix 2. The inclusion criterion was that at least 50% of the sample should have ICD-10 F20 or F22-F29 diagnoses or a DSM diagnosis of a non-affective psychotic disorder. The search retrieved eight studies, several of which were compromised by methodological limitations, namely small sample size (Bendall et al., 2012a; Burns et al., 2011), relatively low percentages of participants with non-affective psychosis (60 and 61%; Aas et al., 2011 and Fisher et al., 2010 respectively), exclusively African American samples (Conus et al., 2010; Ramsay et al., 2011), reliance on unvalidated measures of trauma (Burns et al., 2011; Conus et al., 2010) and exclusion of drug users (Burns et al., 2011). In addition only two of the studies assessed emotional and physical neglect, three assessed parental separation and none institutionalization. In three of the studies, comparisons of prevalence were based on non-psychotic clinical control groups. These studies were conducted by the same research group, and there was overlap between the FEP samples in two studies (Aas et al., 2011 and Fisher et al., 2010).
Two studies reported that childhood adversity was more prevalent in the FEP group (Aas et al., 2011; Mondelli et al., 2011) and one found a significant increase in experience of multiple forms of childhood adversity, but not experience of a single form of childhood adversity, in the FEP group (Fisher et al., 2010). An updated search (July 2015) retrieved 17 FEP studies, including just one case-control study in addition to our own. It remained the case that many studies were subject to methodological limitations. Just five of the 17 studies assessed emotional or physical neglect and only three assessed separation or parental loss (Aas et al., 2011; Conus et al., 2010; Morgan et al., 2007; Fisher et al., 2010; note that these last two used the same sample), which may have reduced overall prevalence rates (median = 74%, range: 44 – 94%) (Aas et al., 2011; Bendall et al., 2012a; Braehler et al., 2013; Burns et al., 2011; Campbell et al., 2013; Conus et al., 2010; Fisher et al., 2010; Mondelli et al., 2011; Ramsay et al., 2011; Spidel et al., 2010; Stain et al., 2014; Ucok A. and Bikmaz S., 2007; Wang et al., 2013). It should also be noted that Stain et al. (2014), who reported the lowest prevalence of childhood adversity, 44%, used the Brief Betrayal Trauma Survey (Goldberg and Freyd, 2006). This uses a very small number of questions to assess sexual and emotional abuse and requires respondents to evaluate their experiences rather than respond to direct questions. This is a method known to decrease disclosure (Dill et al., 1991) and is therefore likely to have resulted in lower prevalence figures. Just one of the additional studies had a control group, which again included people with psychiatric disorders (35% of the sample) (Braehler et al., 2013). The prevalence of childhood adversity is higher in the psychiatric population than in non-clinical populations (Kessler et al., 2010). The median prevalence of different types of adversity in the studies were: sexual abuse, 26%; physical abuse, 24%; emotional abuse, 39%; emotional neglect, 29%; physical neglect, 37% (see figure 5). The median prevalence of parental death/loss was 9% (range: 8-21%) and the median prevalence of parental separation was 42% (range: 41-50%) (Aas et al., 2011; Conus et al., 2010; Fisher et al., 2010). The studies are illustrated in figures 4 and 5.
Figure 4. Childhood adversity prevalence in first-episode psychosis and non-clinical control groups (July 2015).

Figure 5. Prevalence of childhood adversity types in first-episode psychosis (July 2015).
Hill’s criteria for causality

Despite this extensive literature some authors still do not acknowledge that childhood adversity is a risk factor for non-affective psychosis (Castle and Buckley, 2014, p. 35) and some propose that it merely signals the presence of other causal factors (Cutajar et al., 2010; Murray et al., 2013). A brief discussion of this follows, as plausible causality is one of the foundations of this project. The strength of the association between childhood adversity and non-affective psychosis was recently assessed using the Bradford Hill criteria (Bentall et al., 2014), a recognized technique for establishing causality from observed associations in the health sciences (Castle and Buckley, 2014). It is most often used for medical diseases and a few of the criteria are less relevant to psychiatry although they are useful for providing an overview. There are nine criteria, in descending order of importance they are: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (Hill, 1965).

‘Strength’ is the strength of the association, which in most psychosis studies is reported as an odds ratio. In the case of childhood adversity the odds ratio can describe the probability of exposure to a particular form of childhood adversity or to multiple forms. Varese et al.’s (2012) meta-analysis gives an odds ratio of 2.78 (95% CI 2.34–3.31) for exposure to all forms of childhood adversity among people with non-affective psychosis. Two studies of long-term psychosis report odds ratios of 3.43 (95% CI 2.05–5.75) for a combination of two or more forms of adversity (Rubino et al., 2009) and 7.96 (95% CI 3.91–16.17) for a combination of three or more forms of adversity (Shevlin et al., 2007). In comparison with the odds ratios for other factors associated with non-affective psychosis these are strong associations (see Table 1).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Increased risk of psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth complications*</td>
<td>4</td>
</tr>
<tr>
<td>Cannabis use*</td>
<td>2</td>
</tr>
<tr>
<td>Intrauterine infection*</td>
<td>1.2</td>
</tr>
<tr>
<td>Urban living as child*</td>
<td>2.4</td>
</tr>
<tr>
<td>Winter birth*</td>
<td>1.1</td>
</tr>
<tr>
<td>CNV deletions &amp; duplications*</td>
<td>1.15</td>
</tr>
<tr>
<td>TPH gene*</td>
<td>1.18</td>
</tr>
<tr>
<td>Childhood adversity, any</td>
<td>2.8</td>
</tr>
<tr>
<td>Childhood adversity &gt;=2*</td>
<td>3.43</td>
</tr>
<tr>
<td>Childhood adversity &gt;=3*</td>
<td>7.96</td>
</tr>
</tbody>
</table>

Table 1. Risk of non-affective psychosis for different significant risk factors

Notes: CNV Copy number variation, TPH tryptophan hydroxylase.

a (Lewis and Buchanan, 2002, p. 36; Mortensen et al., 1999)

b (Isohanni et al., 2005) and (Lewis and Buchanan, 2002, p. 36)

c (International Schizophrenia Consortium, 2008)

d (Li and He, 2006)

e (Rubino et al., 2009)

f (Shevlin et al., 2007)
‘Consistency’ is a measure of the similarity of findings from different researchers, locations and settings. The results of analyses of the association between childhood adversity and non-affective psychosis are consistent: similar findings have been reported by many research groups and using different study designs. Hill states that the importance of ‘Specificity’ should not be overemphasized as many risk factors, such as cigarette smoke, can cause several diseases and many diseases are multifactorial. Bentall argues that there are specific associations between certain types of adversity and some psychotic symptoms, but the evidence for this is extremely sparse. As mentioned in the section ‘The risk developmental model’, most psychiatric disorders are associated with childhood adversity and therefore one cannot claim that the association is specific to non-affective psychosis.

The ‘temporality’ criterion states that exposure to the putative cause must precede the outcome; this is almost by definition the case for childhood adversity and non-affective psychosis, since exposure to childhood adversity necessarily occurs in childhood whereas psychosis develops in adolescence or adulthood (Leung and Chue, 2000). One large FEP study which explicitly investigated temporality found that sexual and physical abuse preceded psychosis in 98% of cases (Conus et al., 2010). The term ‘biological gradient’ is used to refer to a dose-response effect. There is fairly good evidence that both more frequent exposure to childhood adversity and exposure to more forms of adversity are associated with a higher risk of developing non-affective psychosis. The relevant studies are reviewed in the section ‘Form and amount of childhood adversity’.

The sixth criterion, plausibility, is whether the association makes biological sense. According to Hill (1965) this is not an essential criterion as there should be room for new ideas to emerge; however it is clear that the plausibility criterion is met in our case, since childhood adversity is, by definition, traumatizing and causes a psychological imbalance that is likely to result in pathological disturbance if it is not dealt with. In addition, childhood adversity has been shown to have similar effects on brain structure and functioning to those observed in people with non-affective psychosis (Read et al., 2014).

‘Coherence’ refers to the fact that the findings from different fields, such as biology, epidemiology and case studies, should be consistent. There is no evidence against such coherence in the case of the link between childhood adversity and non-affective psychosis. The ‘experiment’ criterion is that removal of the putative cause should remove the outcome and there is some evidence for this in the case of childhood adversity and non-affective psychosis. A population study found that psychotic
symptoms disappeared when bullying stopped (Kelleher et al., 2013) and studies of traumatized children have shown that removal from traumatizing environments reduces later psychiatric, cognitive and emotional difficulties (Perry, 2002; Teicher et al., 2003). The ‘analogy’ criterion is met if exposure to similar factors produces similar effects, such as toxins causing birth defects, which on the contrary to specificity, increases the likelihood of childhood adversity causing psychosis, as it increases the risk of depression (Matheson et al., 2012), anxiety and bipolar disorder (Maniglio, 2013) and PTSD (Gerson and Rappaport, 2013). In summary, the evidence relating to the link between childhood adversity and non-affective psychosis satisfies the majority of the Hill criteria and the criterion for which the evidence is weakest, specificity, is arguably not essential. Nevertheless, causality cannot be firmly established unless a mechanism is identified and the evidence relating to this is discussed in the section ‘Form and amount of childhood adversity’.

**How does form and amount of childhood adversity affect FEP?**

It is unclear whether some forms of childhood adversity increase the risk of developing non-affective psychosis more than others. Various case-control and prospective studies have shown that various forms of childhood adversity increase the risk of psychosis, including parental loss/separation (Aas et al., 2011; Agid et al., 1999); emotional and physical neglect (McCabe et al., 2012; F. Varese et al., 2012); emotional abuse (McCabe et al., 2012; F. Varese et al., 2012; Whitfield et al., 2005) and physical abuse and sexual abuse (Cutajar et al., 2010; Elklit and Shevlin, 2011; Fennig et al., 2005; McCabe et al., 2012; F. Varese et al., 2012). Some of these studies found that only some forms of childhood adversity increased the risk of psychosis (Aas et al., 2011; McCabe et al., 2012). This body of research is methodologically sound, since it consists of register studies, which are not subject to recall bias, large population studies, whose findings are quite robust and well-matched case-control studies; however none of the studies provides good evidence for the specificity of the association between a particular form of childhood adversity and non-affective psychosis as none controlled for the potential confounding effects of exposure to other forms of childhood adversity.

There are other studies, which attempted to address this by adjusting for the effects of other forms of adversity when considering the risk associated with one particular form of adversity, but the results are inconsistent. Bebbington et al. found that sexual abuse and serious injury, illness or assault were the strongest predictors of psychosis (Bebbington et al., 2004), whereas others reported that the strongest predictors were sexual and emotional abuse (Daalman et al., 2012); physical abuse
and parental discord (Rubino et al., 2009); physical abuse and violence at home (Shevlin et al., 2007) or physical abuse from the mother (Fisher et al., 2010). One further study which examined the relationships between various types of adversity and different psychotic symptoms in the general population found that sexual, physical or emotional abuse and emotional neglect contributed similarly to risk for non-affective psychosis (van Nierop et al., 2014a). In summary, it remains unclear whether certain forms of adversity play a greater role in non-affective psychosis than others.

One explanation for this pattern of findings is that the type of childhood adversity does not strongly influence risk of psychosis. As mentioned above, trauma researchers have defined trauma as an overwhelming event that disturbs an individual’s psychological balance for an extended period (Levine and Frederick, 1997; Payne et al., 2015). The more overwhelming the event and the longer it lasts, the greater the dysfunction experienced by the organism consequently. It has long been recognized that all forms of abuse or neglect are potentially traumatizing (De Bellis, 2001) and that the severity and frequency of the abuse are important determinants of functioning in the traumatized child (Manly et al., 1994). Severity and persistence are the factors which separate trauma from everyday accidents (Grayson J., 2006; Perry, 2002; Teicher et al., 2003). Considering the relationship between childhood adversity and psychosis in terms of a dose-response effect, and the sense in which the consequences of trauma reflect a dose-response relationship suggests different mechanisms from those one might consider if focusing on differences between different forms of. Such mechanisms might include the limbic-hypothalamic-pituitary-adrenal (LHPA) axis response, which is seen altered in those exposed to neglect and abuse (Bruce et al., 2009; Perry and Szalavitz, 2007), increased locus coeruleus activity, which accompanies fight, flight and freeze responses (De Bellis, 2001; Perry and Pollard, 1998) and psychological responses such as feelings of social defeat, which have been hypothesized to mediate the relationship between childhood adversity or other social risk factors and psychosis (Selten et al., 2013; Selten and Cantor-Graae, 2005). As well as informing models of the relationship between childhood adversity and non-affective psychosis the existence of gradient or dose-response relationship is important because it provides evidence of a causal relationship (Hill, 1965). Three studies showed that the risk of developing non-affective psychosis increases with increases in the number of forms of adversity to which one is exposed (Heins et al., 2011; Rubino et al., 2009; Shevlin et al., 2007). A large mixed FEP study (61% non-affective and 39% affective psychosis) found no clear difference in the risk associated with exposure to one or multiple forms of adversity or abuse by one or two caregivers (Fisher et al.,
2010) and a study of non-affective FEP found no association between positive psychotic symptoms and the number of types, severity or frequency of childhood adversity as represented by total CTQ score (Sahin et al., 2013). In addition, several population studies have found a positive association between the number of forms of childhood adversity to which an individual is exposed and the risk of hallucinations (Anda et al., 2006) or hallucinations and delusions (Arseneault et al., 2011; Heins et al., 2011; Lataster et al., 2006).

Exposure to a greater ‘amount’ of adversity increases the risk of psychosis, where ‘amount’ refers to the severity, duration or number of forms of adversity. In psychosis studies, it usually represents the last, but several of the assessment instruments include measures of severity and duration. Assessment methods are considered further in the section ‘Form and amount of childhood adversity’.

**Perceived support and family contact in FEP**

Resilience is defined as the ability to adjust to and overcome hardship (Everly and Lating, 2012, chap. 7). Hence, resilience factors are not merely protective factors, but underlie the differential responses that people have to adversity. They may help explain how some people evade psychiatric disorders despite exposure to severe childhood adversity. Resilience factors may comprise genetic variations, changes caused by previous experiences, or later supportive factors such as helpful relationships (Rutter, 2006). This project concerned the factors perceived social support during childhood and current family contact. Resilience factors has been prominent in child and adolescent psychiatry (Sameroff, 2006) and in the field of PTSD, but less so in adult psychosis research. Perceived support is considered a resilience factor for PTSD, as it has been to decrease the risk of PTSD in response to trauma; a meta-analysis of 11 studies concluded that lack of social support after a traumatizing event was associated with a diagnosis of PTSD (Brewin et al., 2000). Results from other fields include a birth-cohort study which found that lack of paternal affection and support during childhood increased the risk of developing various psychiatric disorders in late adolescence (Lynskey and Fergusson, 1997) and a study of newlyweds which found that perceived current support was negatively associated with trauma symptoms as measured by the Trauma Symptom Inventory (Briere, 1995), which includes symptoms of anxiety, depression and dissociation (Evans et al., 2013). No clinical studies of non-affective psychosis have explicitly examined the effects of perceived support. However, a recent population study reported that people with higher levels of objective or perceived support had fewer delusion-like experiences (Saha et
al., 2012). A recent meta-analysis concluded that people with non-affective psychosis have smaller social networks than non-clinical populations (Gayer-Anderson and Morgan, 2013), and this seems to reflect a lack of close confidants rather than a lack of acquaintances (Macdonald et al., 2000). Number of confidants is closely related to perceived support as the latter explicitly represents the availability of people in whom one can confide; one might therefore conclude that people with non-affective psychosis receive less social support than the general population. We have found no studies exploring perceived support during childhood in people with non-affective psychosis, but we hypothesize that levels are lower than for non-clinical controls on basis of the evidence listed above and a recent study of people with delusions, which found that delusional experiences diminished in the context of good relationships due to an increase in cognitive flexibility (Jolley et al., 2014). This suggests that perceived lack of support may play a role in the development of psychosis.

As discussed in paper 1, it appears that the majority of the childhood adversity reported by people with FEP occurs within the family (Trauelsen et al., 2015). Furthermore, the family network seems to be a major source of support for people with FEP (Jolley et al., 2014).

In summary, this part of the project sought to examine how current family contact was related to experience of childhood adversity and to explore whether perceived support during childhood affected the risk of developing psychosis directly and via an interaction with childhood adversity.

**Psychosocial consequences of childhood adversity**

Premorbid functioning has recently been shown to be associated with childhood adversity. Stain et al. (2014) showed that people with FEP who had experienced childhood adversity had worse academic and social adjustment during most premorbid periods than their counterparts. Conus et al. (2010) found that exposure to sexual abuse or physical abuse was negatively associated with premorbid social adjustment and Schenkel et al. (2005) reported that in people with long-lasting psychosis childhood adversity was associated with difficulties at school and with peers during the premorbid period. These findings suggest that deterioration in premorbid functioning may not, as researchers have often suggested, be caused merely by neurodegenerative encephalopathy (Allen et al., 2013; Larsen et al., 2004), in which case modification of the neurodegenerative theory of psychosis is needed.

Childhood adversity also seems to affect functioning in later life. Social and global functioning and occupational or educational functioning are the domains of functioning most commonly considered.
Population studies have found evidence of a negative association between childhood adversity and employment rates (Widom, 2000) and educational achievement (Boden et al., 2007). To date the results from psychosis studies have been sparse and mixed. One study of people with non-affective psychosis found a negative association between childhood adversity and current overall functioning but not current social functioning (Gil et al., 2009), whereas a FEP study found that childhood adversity was associated with social activity (Duhig et al., 2015). One schizophrenia study found that childhood sexual abuse was negatively associated with functioning in some social domains (intimacy and role functioning) but not others (Lysaker et al., 2001). An Ultra High-Risk follow-up (at 2-14 years) study found a negative association between bullying - but no other forms of childhood adversity - and current functioning (Addington et al., 2013). A follow-up study of an ultra-high risk group (at 2-14 years) found that in both transitioned and non-transitioned individuals, total CTQ score predicted social and vocational functioning, unlike the other potential predictive factors investigated, including DUP and baseline symptoms (Yung et al., 2015). Just 66% of the Duhig sample had a non-affective psychosis and Lysaker et al. only included sexual abuse, which makes it hard to generalize their findings to other samples of people with non-affective psychosis. In view of these methodological shortcomings and the mixed results there is a need for further research into the relationship between childhood adversity and current functioning.

Evidence on the relationship between childhood adversity and occupational functioning is similarly mixed and subject to methodological concerns. Conus et al. only assessed physical and sexual abuse and Campbell et al. used a small sample. Both Duhig et al. (2015) and another small FEP study (Campbell et al., 2013) found that childhood adversity was unrelated to current employment status, whilst a larger FEP study of 658 people found that exposure to physical and/or sexual abuse was negatively associated with current employment (Conus et al., 2010). In addition, a small study of people with schizophrenia found that childhood adversity was positively associated with current employment (Spence et al., 2006). It should be noted, however, that this study excluded people with PTSD – the population which has been found to have the highest rate of childhood adversity - who represent up to 39% (95% CI 23–55%) of people with FEP (Bendall et al., 2012b), and is thus rather unrepresentative. There are only two FEP studies which have examined the relationship between years of education and childhood adversity; they found it to be weak or non-existent (Ramsay et al., 2011; Ucok A. and Bikmaz S., 2007). In summary, it is unclear whether childhood adversity is related to global functioning, educational achievement or occupational status in people with non-affective psychosis.
We sought to examine how various forms of childhood adversity were related to premorbid trajectory and to social outcome factors in a larger representative sample.

The interplay of metacognition, childhood adversities and psychosis

Metacognition literally means ‘thinking about thinking’ and the term is used to refer to the recognition and interpretation of mental states in oneself and others and to the use of this knowledge to manage psychological problems (Lysaker et al., 2013, 2005; Semerari et al., 2003). Metacognition is regarded as an evolutionary adaptation that has enabled humankind to create and live in highly complex civilisations (Brüne and Brüne-Cohrs, 2006). It is related to theory of mind (ToM), mentalization and many aspects of social cognition (Penn et al., 2008). ToM is the ability to recognize mental states in oneself and others, and to understand that other people may view situations differently (Brüne, 2005; Sprong et al., 2007). The concept of mentalization is derived from ToM but more closely resembles metacognition. It is the ability to interpret the behaviour of oneself and others in terms of different mental intentions (Bateman and Fonagy, 2004; Brüne, 2005; Choi-Kain and Gunderson, 2008; Sprong et al., 2007). Social cognition is a broad construct related to processes of social interpretation. In psychosis research social cognition especially implicates ToM, emotion recognition and attributional style, i.e. the attribution of responsibility for an event to oneself or others (Penn et al., 2008).

ToM is most often studied using laboratory experiments, whereas mentalization and metacognition are investigated using personal narratives and social cognition via many different methods. ToM can be regarded as the source of the other three concepts, which are broader, where mentalization and metacognition are the most strongly rooted in everyday life experiences. ToM was first extensively studied in people with autism spectrum disorders, and it was discovered that metacognitive deficits could exist in the absence of cognitive deficits (Brüne and Brüne-Cohrs, 2006), a finding later extended to people with non-affective psychosis (Brune, 2005; Penn et al., 2008). Subsequently they were found in people with depression and bipolar disorder (Hoertnagl and Hofer, 2014), personality disorders (Domes et al., 2009; Fonagy and Bateman, 2008) and non-affective psychosis (Backasch et al., 2013; Bora et al., 2009; Bora and Pantelis, 2013; Smeets-Janssen et al., 2013). They are most severe in people with non-affective psychosis (Bodnar et al., 2014; Hofer et al., 2010; Penn et al., 2008); metacognitive deficits are believed to be a core feature of the disorder and one of the main problems of this population (Brune, 2005; Frith, 1992; Lysaker et al., 2010a, 2010b; Penn et al., 2008; Sprong et al., 2007).
Positive and negative symptoms are the most definitive features of non-affective psychosis and were associated with metacognition as early as 1992 (Frith, 1992). Subsequently, the association with negative symptoms has been confirmed in a small number of non-affective FEP studies (Macbeth et al., 2014; McLeod et al., 2014; Vohs et al., 2014) and several studies of long-lasting psychosis (Hamm et al., 2012; Lysaker et al., 2005; Nicolò et al., 2012; Rabin et al., 2014; Vohs et al., 2014). Six of these studies used correlation analysis (Hamm et al., 2012; Lysaker et al., 2005; Macbeth et al., 2014; McLeod et al., 2014; Nicolò et al., 2012; Rabin et al., 2014; Vohs et al., 2014) whilst two used prospective analysis to show that baseline metacognition predicted negative symptom severity at a six-month follow-up (Hamm et al., 2012) or at six and twelve-month follow-ups (McLeod et al., 2014). This last study also included the known predictors of negative symptoms premorbid adjustment, DUP and baseline symptom levels.

The pattern of findings is less consistent in the case of positive symptoms. In Hamm et al.’s study baseline metacognition did not predict positive symptom severity six months later, but in McLeod’s (2014) it was a predictor of positive symptoms at both the six- and twelve-month follow-ups. Hamm et al. (2012) found that metacognition and positive symptoms correlated, whereas Lysaker et al. (2005) and McLeod et al. (2014) found that positive symptoms correlated with fewer metacognitive items than did negative symptoms. Three studies found no correlations involving metacognition and positive symptoms (Macbeth et al., 2014; Nicolò et al., 2012; Vohs et al., 2014). Some of the negative findings may be due to methodological limitations, such as small sample size (N = 34) and very low positive symptom levels (MacBeth et al., 2014), small sample size (N = 45) and exclusion of unstable service users (Nicolò et al., 2012).

The findings with respect to ToM are quite similar; there are more reports of associations with negative symptoms than positive symptoms (Harrington et al., 2005). We suggest that the mixed findings in relation to positive symptoms reflect the failure to control for variance in negative symptoms in many studies (Hamm et al., 2012; Macbeth et al., 2014; McLeod et al., 2014; Nicolò et al., 2012). We sought to examine this question by comparing associations between different positive and negative symptom profiles and various metacognitive abilities. We also sought to determine whether childhood adversity predicted positive and negative symptom levels, since findings from previous FEP studies have been mixed (Conus et al., 2010; Ramsay et al., 2011; Ucok A. and Bikmaz S., 2007) and a recent meta-analysis concluded that childhood adversity predicted the persistence of psychotic symptoms (Trotta et al., 2015). To avoid confounds the MANOVA included established predictors of positive and negative symptoms, i.e. premorbid...
adjustment (Chang et al., 2013; MacBeth and Gumley, 2008; Simonsen et al., 2010) and DUP (Boonstra et al., 2012; Crumlish et al., 2009; White et al., 2009). Only one of the aforementioned studies (Rabin et al., 2014) investigated whether people with non-affective psychosis showed impaired metacognition relative to non-clinical controls although this should be the starting point for any exploration of metacognition in this population. We therefore sought to assess metacognitive function in our non-affective psychosis group and compare it with metacognition in a well-matched non-clinical control group.

Metacognitive abilities develop throughout childhood and are influenced by environmental factors, especially interactions with primary caregivers (Fonagy and Target, 1997; Ontai and Thompson, 2008; Tager-Flusberg, 1999; Yagmurlu et al., 2005). Retrospective reports have found parental rejection to predict poorer social cognition in adults (Romero-Martinez 2013) and longitudinal data have shown that securely attached children have better ToM abilities compared to insecurely attached children (Meins et al., 1998). Accordingly, neglect and abuse have been suggested to cause poorer representations of self and others as part of the pathway to psychosis (MacBeth et al., 2011; Rajkumar, 2014). This is supported by a case-control study that found that children placed in institutional care due to maltreatment had poorer ToM abilities and emotion understanding than non-maltreated children (Pears and Fisher, 2005). One study of metacognition included adversity and found that people reporting sexual abuse had high Self-reflective skills but low Awareness of Mind of the Other (P.H. Lysaker et al., 2011). The study did not measure other adversities known to increase the risk of psychosis why studies with comprehensive adversity assessment are required. In addition, it has been found that a high level of stress increases activity in the basic areas of the brain while it decreases the cortical activity necessary for metacognitive activity (Cohen, 2014; Porges, 2004). Based on this literature we expected to find that metacognitive abilities were negatively associated with number of childhood adversities.

**Overview of the study variables**

To provide an overview of this study the relevant variables have been depicted in figure 6. This illustrates changes in functioning from childhood through to adulthood in the case of an individual who develops first-episode psychosis. Functioning fluctuates throughout life and is first represented as premorbid adjustment, i.e. academic and social functioning before the onset of psychosis; then in terms of global functioning in the year prior to starting treatment and finally in terms of academic achievement, vocational and everyday functioning and metacognitive abilities at the time of
interview, i.e. a median three months into treatment. This study explored the relationships between childhood adversity and all these different measures of function, alongside metacognition and in relation to positive and negative symptoms. Furthermore, childhood adversity and perceived childhood support were examined as risk and resilience factors for psychosis.

**Figure 6. Overview of the study variables.**

![Diagram](image)

Notes: The figure has been inspired by figure 1 in (Howes and Murray, 2014)

**Aims**

The motivation for the study is based on the following considerations. As well as increasing the risk of developing non-affective psychosis, childhood adversity may affect people with the disorder in various other ways. First of all, it is important to know how prevalent childhood adversity are in representative samples. Second, we should strive to establish whether the various forms of childhood adversity are causal factors or proxies for causal factors and what characteristics of childhood adversity are responsible for its relationship with non-affective psychosis. This information could be used to guide future research. Third, the relationships between the various forms of childhood adversity and important characteristics of non-affective psychosis should be examined, in order to determine whether childhood adversity is responsible for symptoms or features of the disorder that are currently assumed to be caused by other factors. Such features
include premorbid and present functioning and metacognitive impairment. Specific objectives and hypotheses were developed to guide the investigation of these issues.

**Objectives and hypotheses**

i. To examine the prevalence of childhood adversity in people with non-affective FEP and a matched non-clinical control group.

ii. To examine the importance of the type and number of childhood adversities for the risk of psychosis.

iii. Childhood adversities will negatively affect premorbid trajectories, years of education and global, occupational and living functioning.

iv. To examine whether perceived support during childhood decreases the risk of psychosis and whether perceived support and family contact is associated with childhood adversity.

v. The FEP group will have lower metacognitive abilities than the non-clinical control group.

vi. Metacognitive abilities will be negatively associated with number of childhood adversities.

vii. Poorer metacognitive abilities and more childhood adversities will be associated with high levels of positive and negative symptoms independently and together.

**Method and material**

**Study design**

The study had a cross-sectional case-control design. The participants with FEP were part of an intervention study comparing individual family-work with multiple family-work. It strived to include everyone who entered the early intervention service (OPUS) (Petersen et al., 2005) in Region Zealand, Denmark, from April 1st 2011 to April 1st 2013. The catchment area population was 816,359. Participants were assessed consecutively. The control persons were assessed for the present study alone. They were recruited through advertisement in newspapers, at educational institutions, libraries and sport clubs and by word of mouth. They were included from October 1 2013 to May 22 2014. They were matched 1: 1 by gender, age (+/-1 year) and highest parental education (+/-1 one on a 5 point scale). To minimize the interviewer’s influence on the interviewee,
the IPII was the first interview to be performed for both participant groups.

**Participants**

**FEP group**

The criteria for entering OPUS at the time of recruitment was a diagnosis of non-affective psychosis (F20-F29, except F21) and being 18-35 years of age. Exclusion criteria were a previous diagnosis of psychosis. Substance abuse was not an exclusion criterion. Additional criteria for the study were sufficient Danish skills for the interview.

**Control group**

Inclusion criteria were living in Region Zealand, Denmark and being 17 to 34 years of age. Exclusion criteria were any previous psychiatric disorder and insufficient Danish skills to complete the interview. Substance abuse was not an exclusion criterion.

**Clinical assessment instruments**

**Psychopathology**

The OPCRIT diagnostic system was used to obtain ICD-10 diagnoses, based on patient records and a Positive and Negative Symptom Scales (PANSS) interview (Kay et al., 1987). The latter was extended to include life-long symptoms (McGuffin et al., 1991). For analyses, we used the five factor categorization suggested and validated by van der Gaag (van der Gaag et al., 2006). A psychologist or medical doctor trained by a senior psychiatrist administered the instruments. Control participants were screened with the Mini International Neuropsychiatric Interview (MINI) 6.0 for any prior and present psychiatric diagnoses (Sheehan et al., 2008). Anne Marie Trauelsen administered all the control group assessment. Psychiatric illness in first-degree relatives included depression, bipolar, autism and psychotic disorders. These were assessed by interview, either of the person in question or for the FEP group a parent.

**Childhood adversity and perceived support**

The Danish validated version of the Childhood Trauma Questionnaire (CTQ) was used for adversity assessment (Bernstein et al., 2003; Bernstein and Fink, 2011). The CTQ consists of five subcategories, each represented by five questions. The CTQ subcategories were dichotomized to include severe and extreme trauma by using the cut-off scores moderate/severe as suggested by
Bernstein et al. (Bernstein and Fink, 2011). They were six for males and females for sexual and physical abuse, eight for males and ten for females for emotional abuse, seven for males and females for physical neglect, and 13 for males and 12 for females for emotional neglect. Separation and institutionalization were assessed with the validated Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005; Smith et al., 2002). Separation that was primarily due to divorce was not included. Number of adversities ranged from zero to seven and comprised the five CTQ subcategories, separation and institutionalization. For age of trauma, we used the Brief Betrayal Trauma Survey, which only assesses sexual, physical and emotional abuse and not neglect (Goldberg and Freyd, 2006). Perceived support during childhood and adolescence was assessed with the CECA.Q. They read “Did you have any adults you could talk to about your problems or feelings, as a child and teenager?” and “Did you have any peers you could talk to about your problems or feelings, as a child and teenager?” Family contact was based on the Lehman Quality of Life Interview, translated by the TIPS research group (Lehman, 1988; Melle et al., 2010). Family contact concerned the year prior to treatment and was assessed with a 5-point scale ranging from 1 (everyday) to 5 (never).

**Premorbid and current functioning**

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was used for assessment of premorbid social and academic adjustment. The PAS has shown good validity and reliability (van Mastriet and Addington, 2002). The social and academic parts of the scale have been found to be associated with different variables and is therefore recommended to be considered as independent factors (MacBeth and Gumley, 2008). The different PAS periods are childhood (0-11 years), early adolescence (12-15 years), late adolescence (16-18 years) and adulthood (19- years).

Highest parental vocational education was chosen as a matching parameter due to its association with both childhood adversities and psychosis (Croudace et al., 2000; Sidebotham and Heron, 2006). It was measured on a 5-point scale. Years of education for the participants referred to elementary school and high school and not vocational or university education.

The Global Assessment of Functioning scale (GAF) was used to assess functioning the year prior to treatment entry and represents the best month of that year (Karterud et al., 1998; Pedersen et al., 2007). Living and occupational status were based on the Lehman Quality of Life Interview, translated by the TIPS research group (Lehman, 1988; Melle et al., 2010). Living status concerned status at treatment start and was assessed with a 4-point scale: 1. Independent 2. Independent w. support, 3. Institution and 4. Without housing. Occupational status consisted of six categories,
which were redefined as 1. High level (working, studying or homeworking), 2. Intermediate (available) and 3. Low level (receiving welfare (pension or sick leave)).

**Indiana psychiatric illness interview (IPII)**

The IPII is a semi-structured interview where the interviewees are asked to talk about their life. This includes their life story; the psychiatric problems that they may or may not think they have, and how they have been affected by them; how they control and are controlled by these problems; how they are affected by and affect other people; and how their future will be (Lysaker et al., 2002). The control participants go through the same line of questioning, but instead of psychiatric problems, they are asked about psychological difficulties that have occurred within the last two years. The interviewer encourages free speech and provides a minimal amount of direction. The interview lasts about 30 minutes and the responses are transcribed subsequently.

**Metacognition assessment scale-abbreviated (MAS-A)**

MAS-A (Lysaker et al., 2005) is an elaboration of the metacognition assessment scale (MAS) which was developed for metacognitive assessment in psychotherapy (Semerari et al., 2003). The MAS-A brings a dimensional structure to the original MAS and demands a presence of lower order metacognitive skills before the higher scores are awarded. The ratings were based on the IPII transcripts and measured the presence of observations and elaborations conveyed by the interviewees.

The MAS-A consists of the four subscales Self-reflectivity, Awareness of the Mind of the Other (AoM), Decentration and Mastery. Self-reflectivity consists of nine levels, which range from identifying to integrating knowledge about oneself with the identification of affective and cognitive operations as a benchmark for achieving higher ratings. AoM consists of seven levels, which range from identifying to integrating knowledge about others, in a progressively more complex way. Decentration consists of three levels. It reflects a person’s ability to understand that other people lead their lives and interact with each other independent of the interviewee. Mastery consists of nine levels and concerns the ability to use understanding of self and others to solve or overcome psychological difficulties. The MAS-A total score is the sum of the four subscales.

The MAS-A has been found to have good inter-rater reliability with intra-class coefficients ranging from 0.71 to 0.91 (Lysaker et al., 2005).
**Duration of untreated psychosis**

DUP was defined as having a psychotic symptom score equal to or above 4 for the whole day a week in a row or several times a week for several weeks, as described by (Melle et al., 2006). Any periods without symptoms were subtracted from the DUP. The DUP was considered over when antipsychotic medication, OPUS or inpatient treatment started. Any uncertainties regarding DUP ratings were resolved between the authors and information drawn from electronic patient files and staff. Test–retest reliability for this method of determining DUP from has been found to be good (intraclass coefficient $r = .96$, p < 0.01) (Larsen et al., 1998).

**Ethics**

All participants received oral and written study information. For persons with FEP it was clearly stated that they could withdraw their consent at any time and that participation had no impact on their treatment. Control persons received DKK 400 equal to EURO 54 as compensation for their time and contribution. The protocol was submitted to the Regional Ethics Committee and pre-approval was found unnecessary as it only implicated questionnaires and interviews. The Data Protection Council, Region Zealand, approved data management (journal no. 12-000660).

**Statistical analyses**

The IBM SPSS Statistics for Windows, Version 22.0 was used for all analyses. Frequency graphs for continuous measures were inspected visually to determine approximation of the normal distribution. The Student’s t-test and the Mann–Whitney $U$ test were used for comparisons between the FEP and the control group and Spearman Rank Correlation analyses were used for correlation analyses. All significance tests were two-tailed and the $\alpha$-level set at 0.05.

For paper 1, a priori binary logistic regression analyses were performed with psychosis as the dependent variable and age, gender, parents’ socioeconomic status, first-degree psychiatric illness and adversities as covariates. Significant adversities were included in the final model to fit the best predictive model and investigate independent adversity influence.

For paper 2, the K-Means cluster analysis was applied for the identification of groups based on premorbid social and academic change scores. It seeks to create groups with minimal difference within groups relative to between groups (Dillon and Goldstein, 1984). As suggested by Larsen et al., the clusters were identified by change from childhood to the last PAS score, which was at least six months before psychosis onset. The ratings in childhood were labelled good ($<1.50$),
intermediate (1.50–2.99) or poor (≥3.00), while the changes were labelled stable (<1.00), slightly deteriorating (1.00–1.99) and clearly deteriorating (>2.00) (Larsen et al., 2004). There were no clear outliers. The best number of groups was based on the number of distinct patterns identified by the analyses, as suggested by (Larsen et al., 2004). It was three for the social PAS and four for the academic. A one-way analysis of variance (ANOVA) and the Kruskal-Wallis test (for non-normal distributions of the number of adversities) was performed to test for differences between the groups on number of adversities.

For paper 3, K-Means cluster analysis was applied for the identification of groups based on standardized positive and negative symptom clusters. Two outliers were excluded from the cluster analysis, as they were too influential; they were manually allocated to their subgroups subsequently. A one-way multivariate analysis of variance (MANOVA) was performed to compare the groups on metacognition, number of adversities, DUP and premorbid social and academic adjustment. Based on the Box’s M value of 29.14 and associated value of 0.99 the covariance matrices between the groups were assumed to be equal for the purposes of the MANOVA (Huberty, C. J. and Petoskey, M. D., 2000).

For the regression analyses, ANOVAs and MANOVAs, multicollinearity was not an issue due to generally low correlations, and variances were assumed equal due to non-significant Hosmer-Lemeshow goodness-of-fit tests.

**Interrater reliability**

Seventeen PANSS interview videos and vignettes were randomly drawn from the FEP group and rated by four trained clinicians independently. Twenty IPII transcripts were randomly drawn from both the FEP and control group and were independently rated by Anne Marie Trauelsen and Jens Einar Jansen. The results are presented in table 2. Most of the factors have excellent reliability >.75, while the GAF 1 year and PANSS excitative have fair-to-good reliability 0.40-0.75 (Fleiss, 2011).
Table 2. Inter-rater reliability based on randomly drawn cases

<table>
<thead>
<tr>
<th>Scale</th>
<th>ICC</th>
<th>95% Min</th>
<th>95% Max</th>
<th>F test</th>
<th>Signifiks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS-A FEP group</td>
<td>0.884</td>
<td>0.54</td>
<td>0.92</td>
<td>8.65</td>
<td>0.000</td>
</tr>
<tr>
<td>MAS-A control group</td>
<td>0.867</td>
<td>0.66</td>
<td>0.95</td>
<td>7.52</td>
<td>0.003</td>
</tr>
<tr>
<td>GAF f 1 year</td>
<td>0.818</td>
<td>0.6</td>
<td>0.93</td>
<td>7.33</td>
<td>0.000</td>
</tr>
<tr>
<td>DUP</td>
<td>0.939</td>
<td>0.87</td>
<td>0.98</td>
<td>18.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Positive component</td>
<td>0.811</td>
<td>0.60</td>
<td>0.92</td>
<td>6.44</td>
<td>0.000</td>
</tr>
<tr>
<td>Negative component</td>
<td>0.896</td>
<td>0.77</td>
<td>0.96</td>
<td>12.40</td>
<td>0.000</td>
</tr>
<tr>
<td>Depressive component</td>
<td>0.859</td>
<td>0.71</td>
<td>0.94</td>
<td>7.64</td>
<td>0.000</td>
</tr>
<tr>
<td>Excitative component</td>
<td>0.639</td>
<td>0.29</td>
<td>0.85</td>
<td>3.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Cognitive component</td>
<td>0.811</td>
<td>0.61</td>
<td>0.92</td>
<td>5.25</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: The symptom components are based on the five-factor model by van der Gaag (van der Gaag et al., 2006)

Results

General sample description

There were 194 eligible participants with FEP of which 101 (52 %) were included and matched with 101 control participants. The exclusions were due to a lack of desire to participate (N=51); withdrawal of consent after the first interview (N=14); failure to obtain contact (N=18); insufficient Danish skills (N=3) and due to a delayed inclusion of the CTQ in the protocol (N=11). There were more females (44 % compared to 53 %, $\chi^2 = 7.5, p < 0.01$) and fewer people with schizophrenia in the excluded group (67 % compared to 91 %, $\chi^2 = 26.9, p < 0.001$). The median age was not statistically different for the excluded persons (Mann-Whitney U 4120, $p = 0.053$).

There were additional missing data for different variables, which are presented and explained in the separate papers. Of the control candidates, 16 were excluded because of depression (N=9), hypomanic or manic episodes (N=4), anxiety disorder (N=2) and pre-diagnosed ADHD (N=1). The socio-demographic and clinical data for the FEP and control group are presented in table 3.
Table 3. Sociodemographic data for the FEP and control group.

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>FEP, n (%)</th>
<th>Controls, n (%)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (74)</td>
<td>75 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (26)</td>
<td>26 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>22.5 (18 - 34)</td>
<td>22 (18 - 33)</td>
<td>U=5060*</td>
<td>0.931</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Danish</td>
<td>93 (92)</td>
<td>98 (97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black African</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not finished public school</td>
<td>5 (5)</td>
<td>0</td>
<td>64.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Public school (9-10 years)</td>
<td>68 (68)</td>
<td>19 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gymnasium (12-13 years)</td>
<td>13 (13)</td>
<td>57 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University/completed vocational education</td>
<td>14 (14)</td>
<td>25 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of education</td>
<td>10.16 (1.27)</td>
<td>11.79 (1.00)</td>
<td>U=1690*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td>3.19</td>
<td>0.527</td>
</tr>
<tr>
<td>Lower skilled</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher skilled</td>
<td>38 (38)</td>
<td>40 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer theoretical</td>
<td>28 (28)</td>
<td>28 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>7 (7)</td>
<td>13 (13)</td>
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</tr>
<tr>
<td>Living status</td>
<td></td>
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</tr>
<tr>
<td>Independent</td>
<td>73 (73.70)</td>
<td>101 (100)</td>
<td>30.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Independent w. support</td>
<td>9 (9.10)</td>
<td></td>
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</tr>
<tr>
<td>Institution</td>
<td>15 (15.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without housing</td>
<td>2 (2.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studying</td>
<td>27 (27)</td>
<td>79 (78)</td>
<td>25.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Working</td>
<td>1 (1)</td>
<td>17 (17)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Available</td>
<td>31 (31)</td>
<td>5 (5)</td>
<td>18.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Welfare</td>
<td>41 (41)</td>
<td>0</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete vocational education</td>
<td>16 (16)</td>
<td>25 (25)</td>
<td>2.16</td>
<td>0.142</td>
</tr>
<tr>
<td>Adult Support (FEP group N=93)</td>
<td>61 (66)</td>
<td>92 (92)</td>
<td>20.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peer Support (FEP group N=92)</td>
<td>47 (51)</td>
<td>95 (95)</td>
<td>47.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metacognition (MAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reflectivity (N= 97)</td>
<td>5.24 (1.50)</td>
<td>5.00 (5.50)</td>
<td>6.33 (1.21)</td>
<td>6.50 (5.00)</td>
</tr>
<tr>
<td>AoM (N= 97)</td>
<td>3.42 (0.95)</td>
<td>3.00 (5.00)</td>
<td>4.02 (0.98)</td>
<td>4.00 (5.00)</td>
</tr>
<tr>
<td>Decentration (N= 97)</td>
<td>1.20 (0.62)</td>
<td>1.00 (3.00)</td>
<td>1.65 (0.59)</td>
<td>1.50 (4.50)</td>
</tr>
<tr>
<td>Mastery (N= 97)</td>
<td>4.74 (1.47)</td>
<td>5.00 (7.00)</td>
<td>5.68 (1.09)</td>
<td>6.00 (5.00)</td>
</tr>
<tr>
<td>Premorbid adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>1.91 (1.4)</td>
<td>1.8 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>2.48 (1.3)</td>
<td>2.3 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUP in weeks</td>
<td>168 (225)</td>
<td>68.0 (1072)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS 5 factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11.6 (4.73)</td>
<td>11.0 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16.3 (6.21)</td>
<td>16.0 (24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>5.03 (1.56)</td>
<td>4.00 (6.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>8.47 (2.81)</td>
<td>8.00 (15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.71 (3.40)</td>
<td>8.00 (14.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: AoM, awareness of the mind of the other
* Mann-Whitney test.
+ The highest parental vocational education for either parent.
\* Fisher’s exact test.
\^ Van der Gaag’s 5 factor model (van der Gaag 2006).
Childhood adversity prevalence

One aim of the study was to determine the prevalence of childhood adversity in people with non-affective FEP and a comparison with a non-clinical control group. The majority of the FEP group (89%) reported at least one childhood adversity compared to a minority of the control group (37%). Moreover, more than half of the FEP group had been exposed to at least three adversities, while this was the case for just seven percent of the control group. The distributions are illustrated in Figure 7.

The frequencies for the different adversities ranged from 24% (sexual abuse) to 63% (emotional abuse) for the FEP group and from two (institutionalization) to 17% (emotional abuse) for the control group, when the only non-significantly different adversity, parental death, was omitted. The median lengths of parental separation and institutionalization were respectively four years (range 0.2–18) and 2.8 years (range 0.01–12). The reasons for separation comprised lack of caretaking ability (10%); parental illness (13%); violence (13%) and abandonment (13%); unknown (5%) and other reasons (46%). The frequencies are presented in Table 4.

Figure 7. Number of adversities in the FEP and control group.
Form and amount of childhood adversity (paper 1)

The aims of paper 1 one was to explore childhood adversity specificity and dose-response effects on the risk of non-affective psychosis. Exposure to at least three childhood adversities increased the risk of psychosis, while the linear trend showed that each additional adversity increased the risk of psychosis 2.6 times. Exposure to four or more childhood adversities increased the risk of psychosis 13 times. This is presented in table 4.

The odds ratios for all childhood adversities except for parental death signified increased risks of psychosis from four to 18 times (p-values < 0.01), while a correction for significant adversities greatly diminished these numbers. Sexual and physical abuse and separation were no longer significant, while the odds ratios for emotional abuse and physical and emotional neglect decreased to between 3.5 and 4.4. Institutionalization decreased from 18 to a corrected odds ratio of 13. The CTQ subcategories, sexual, physical, emotional abuse and emotional and physical neglect, were all significantly correlated with at least two of their kind. Separation correlated with institutionalization and physical and sexual abuse, whereas institutionalization only correlated with separation and physical abuse. The steps of the logistic regression analyses comparing the different types of adversities in the FEP and control groups are presented in table 6 and the correlations in table 5.

Table 4. Comparison of number of adversities between the FEP and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR a</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>One adversity</td>
<td>19 (19)</td>
<td>21 (21)</td>
<td>0.95</td>
<td>0.45-1.98</td>
<td>0.88</td>
<td>7.41</td>
</tr>
<tr>
<td>Two adversities</td>
<td>18 (18)</td>
<td>9 (9)</td>
<td>1.84</td>
<td>0.82-4.87</td>
<td>0.13</td>
<td>2.29</td>
</tr>
<tr>
<td>Three adversities</td>
<td>18 (18)</td>
<td>4 (4)</td>
<td>5.06</td>
<td>1.59-16.17</td>
<td>0.01*</td>
<td>7.49</td>
</tr>
<tr>
<td>Four adversities</td>
<td>11 (11)</td>
<td>1 (1)</td>
<td>12.78</td>
<td>1.56-105</td>
<td>0.02*</td>
<td>5.62</td>
</tr>
<tr>
<td>Five or more adversities</td>
<td>24 (24)</td>
<td>2 (2)</td>
<td>12.95</td>
<td>2.84-59.00</td>
<td>0.001**</td>
<td>10.96</td>
</tr>
<tr>
<td>Linear trend b</td>
<td></td>
<td></td>
<td>2.55</td>
<td>1.91-3.40</td>
<td>&lt;0.001**</td>
<td>39.97</td>
</tr>
</tbody>
</table>

a Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status
bAdversities included are CTQ subcategories, separation and institutionalization before age 18
cLogistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status
dInstitutionalization or foster care.
Table 5. Correlations between childhood adversities in the FEP group.

<table>
<thead>
<tr>
<th></th>
<th>Emotional Abuse</th>
<th>Physical Abuse</th>
<th>Sexual Abuse</th>
<th>Emotional Neglect</th>
<th>Physical Neglect</th>
<th>Institutionalization</th>
<th>Separation</th>
<th>Death of parent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Abuse</td>
<td></td>
<td>.237*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>.280**</td>
<td></td>
<td>.348**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>.502**</td>
<td>.327**</td>
<td></td>
<td></td>
<td>.260**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Neglect</td>
<td>.234*</td>
<td>.225*</td>
<td>.188</td>
<td>.458**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institutionalization</td>
<td>.167</td>
<td>.338**</td>
<td>.130</td>
<td>.039</td>
<td>.122</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separation*</td>
<td>.204*</td>
<td>.250*</td>
<td>.057</td>
<td>.101</td>
<td>.114</td>
<td>.627**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of parent*</td>
<td>.051</td>
<td>.046</td>
<td>-.061</td>
<td>.071</td>
<td>.074</td>
<td>.150</td>
<td>.358**</td>
<td></td>
</tr>
<tr>
<td>Any Adversity</td>
<td>.409**</td>
<td>.232*</td>
<td>.170</td>
<td>.269**</td>
<td>.367**</td>
<td>.171</td>
<td>.253*</td>
<td>.089</td>
</tr>
</tbody>
</table>

*Institutionalization or foster care, separation or death of parent before age 18.
**P<0.05
**P<0.01
<table>
<thead>
<tr>
<th>Type of trauma</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Abuse</td>
<td>24 (24)</td>
<td>4 (4)</td>
<td>8.51</td>
<td>2.30-31.50</td>
<td>&lt;0.01**</td>
<td>10.3</td>
<td>4.13</td>
<td>0.87-19.54</td>
<td>0.073</td>
<td>3.2</td>
<td>5.76</td>
<td>0.99-33.55</td>
<td>0.051</td>
<td>3.8</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>37 (37)</td>
<td>14 (14)</td>
<td>3.53</td>
<td>1.59-7.83</td>
<td>&lt;0.01**</td>
<td>9.6</td>
<td>0.97</td>
<td>0.34-2.78</td>
<td>0.958</td>
<td>&lt;0.01</td>
<td>0.72</td>
<td>0.23-2.28</td>
<td>0.580</td>
<td>0.3</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>64 (63)</td>
<td>17 (17)</td>
<td>7.33</td>
<td>3.54-15.21</td>
<td>&lt;0.001**</td>
<td>28.7</td>
<td>3.27</td>
<td>1.41-7.55</td>
<td>&lt;0.01**</td>
<td>9.91</td>
<td>3.71</td>
<td>1.50-9.20</td>
<td>&lt;0.01**</td>
<td>8.0</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>44 (44)</td>
<td>5 (5)</td>
<td>16.93</td>
<td>5.41-52.98</td>
<td>&lt;0.001**</td>
<td>23.6</td>
<td>3.59</td>
<td>1.20-16.87</td>
<td>&lt;0.05*</td>
<td>5.0</td>
<td>4.44</td>
<td>1.13-17.55</td>
<td>&lt;0.05*</td>
<td>4.5</td>
</tr>
<tr>
<td>Physical Neglect</td>
<td>59 (58)</td>
<td>17 (17)</td>
<td>6.23</td>
<td>2.99-13.00</td>
<td>&lt;0.001**</td>
<td>23.8</td>
<td>2.98</td>
<td>1.27-6.97</td>
<td>&lt;0.05*</td>
<td>6.3</td>
<td>3.45</td>
<td>1.38-6.65</td>
<td>&lt;0.01**</td>
<td>7.0</td>
</tr>
<tr>
<td>Separation</td>
<td>39/95 (41)</td>
<td>7 (7)</td>
<td>7.45</td>
<td>2.78-19.94</td>
<td>&lt;0.001**</td>
<td>16.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.78</td>
<td>0.77-9.98</td>
<td>0.118</td>
<td>2.5</td>
</tr>
<tr>
<td>Death of parent &lt; age 18</td>
<td>7/94 (7)</td>
<td>6 (6)</td>
<td>1.20</td>
<td>0.32-4.53</td>
<td>0.788</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Institutionalization &lt; age 18</td>
<td>23/97 (24)</td>
<td>2 (2)</td>
<td>17.55</td>
<td>2.20-140</td>
<td>&lt;0.01**</td>
<td>7.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.1</td>
<td>1.08-159</td>
<td>&lt;0.05*</td>
<td>4.1</td>
</tr>
<tr>
<td>Any adversity</td>
<td>90 (89)</td>
<td>37 (37)</td>
<td>18.12</td>
<td>7.39-44.43</td>
<td>&lt;0.001**</td>
<td>40.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

OR, Odd ratio; CI, confidence interval

<sup>a</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent’s socio-economic status
<sup>b</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent’s socio-economic status and other CTQ categories.
<sup>c</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent’s socio-economic status, other CTQ categories and separation and institutionalization.

<sup>x</sup> Institutionalization or foster care.

*p<0.05, **p<0.01
Age of trauma and psychosis onset

An extra analysis was performed to explore temporality of childhood adversity and psychosis onset. The mean age of psychosis onset was 17 years (SD 4.7). Age of first trauma was reported for 65 persons. The mean difference from time of first trauma to onset of psychosis was eight years (SD 6.4). For 89 % (n = 58) the occurrence of the first trauma preceded the onset of psychosis. Of the remaining 11 % (n = 7), two had experienced psychotic symptoms for as long as they remembered, and one did not recall when the trauma occurred.

Perceived support (paper 2)

One aim of paper 2 was to examine how perceived support during childhood affects the risk of non-affective psychosis and how this is related to childhood adversities. The control persons reported a greater amount of adult and peer support during childhood than the FEP group did (p-values < .001). One fourth of the FEP group reported that they had had neither adult nor peer support compared to one percent of the control group, while respectively 44 % and 88 % reported to have had both. Adult support was significantly negatively correlated with the number of adversities in both groups, while this was only the case for peer support in the FEP group. The risk of psychosis due to number of adversities decreased one tenth but remained significant when it was corrected for peer support. Uncorrected, peer support decreased the risk of psychosis 17 times (OR 0.06, p<0.001), while the correction for number of adversities decreased the effect to 8.3 times (OR 0.12, p<0.001). The corresponding numbers for adult support were 5.9 times (OR = 0.17, p<0.001) and a non-significant corrected OR. Number of adversities was negatively correlated with face-to-face family contact (r, (97) = -.23, p < 0.05) in the FEP group, while contact by telephone was insignificant (r, (97) = -.19, NS). This data is presented in tables 7, 8 and 9.
Table 7. Correlations between childhood adversities, perceived support and social factors in the FEP group.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. No. of adversities</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2. Adult Support</td>
<td></td>
<td>-0.439&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3. Peer Support</td>
<td></td>
<td></td>
<td>-0.299&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.407&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1,000</td>
<td></td>
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</tr>
<tr>
<td>4. Talking to family&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>-0.188</td>
<td>0.066</td>
<td>0.075</td>
<td>1,000</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5. Seeing family</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.233&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.172</td>
<td>0.125</td>
<td>0.430&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1,000</td>
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<tr>
<td>6. Years of education</td>
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<td></td>
<td></td>
<td></td>
<td>-0.070</td>
<td>0.045</td>
<td>-0.086</td>
<td>0.167</td>
<td>0.148</td>
<td>1,000</td>
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<td>7. Occupational status</td>
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<td></td>
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<td>-0.061</td>
<td>0.090</td>
<td>0.057</td>
<td>-0.094</td>
<td>-0.157</td>
<td>-0.138</td>
<td>1,000</td>
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<td>8. Living status</td>
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<td>-0.182</td>
<td>0.066</td>
<td>-0.065</td>
<td>-0.297&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.353&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.161</td>
<td>0.081</td>
<td>1,000</td>
</tr>
<tr>
<td>9. GAF 1 year</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.215&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.199</td>
<td>0.341&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.118</td>
<td>0.157</td>
<td>0.288&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>10. Social level childhood&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.032</td>
<td>-0.175</td>
<td>-0.208</td>
<td>0.029</td>
<td>-0.087</td>
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<tr>
<td>11. Academic level childhood&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.048</td>
<td>-0.015</td>
<td>0.137</td>
<td>-0.022</td>
</tr>
<tr>
<td>12. Social change&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>-0.016</td>
<td>-0.150</td>
<td>-0.132</td>
</tr>
<tr>
<td>13. Academic change&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>-0.076</td>
<td>-0.239&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>14. First Degree Psychiatric Disorder&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>-0.242&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Notes: Spearman Rank Correlations.
<sup>a</sup> Keep in mind that positive premorbid scores represent worse adjustment.
<sup>b</sup> Talking on the phone
<sup>c</sup> Reported psychosis, bipolar, autism and depression in first degree relatives.
<sup>d</sup> Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).
Table 8. Correlations between childhood adversities, perceived support and social factors in the control group.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1,000</td>
<td>.284*</td>
<td>-.058</td>
<td>.052</td>
<td>.063</td>
<td></td>
<td>.132</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td>.101</td>
<td>-.003</td>
<td>.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
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<tr>
<td>5.</td>
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<td>6.</td>
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<tr>
<td>7.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Notes: Spearman Rank Correlations.
<sup>a</sup> Everyone lived independently.
<sup>b</sup> Reported psychosis, bipolar, autism and depression in first degree relatives.
* Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).
Table 9. Comparisons of childhood adversities between different premorbid trajectories.

<table>
<thead>
<tr>
<th>PAS Social</th>
<th>1 Good stable (N=45)</th>
<th>2 Good deteriorating (N=19)</th>
<th>3 Poor, slightly improving (N=16)</th>
<th>Mean Square between groups</th>
<th>$F(2, 77)$</th>
<th>$p=$</th>
<th>$\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adversities $^a$</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>4.860</td>
<td>1.46</td>
<td>.24</td>
<td>0.20</td>
</tr>
<tr>
<td>PAS academic</td>
<td>1 Intermediate stable (N=38)</td>
<td>2 Good, clearly deteriorating (N=11)</td>
<td>3 Poor, clearly improving (N=4)</td>
<td>4 Good, slightly deteriorating (N=27)</td>
<td>$\chi^2(df=3)$</td>
<td>4.46</td>
<td>.22</td>
</tr>
<tr>
<td>No. of adversities $^b$</td>
<td>2.95 (1.89)</td>
<td>3.27 (2.57)</td>
<td>1.50 (1.00)</td>
<td>2.26 (1.35)</td>
<td>4.46</td>
<td>.22</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Analysis of variance.
$^b$ Kruskal-Wallis test.
Premorbid trajectories, years of education and global, occupational and living functioning (paper 2)

Paper 2 also aimed to identify different premorbid trajectories in order to examine their relation to childhood adversities in addition to an examination of the relations between childhood adversity and important social factors. Four premorbid academic adjustment trajectories were recognized by the K-mean cluster analysis. They comprised 1. intermediate stable (N=38), 2. good, clearly deteriorating (N=11), 3. poor, clearly improving (N=4) and 4. good, slightly deteriorating (N=27). None of the trajectories was associated with more childhood adversities ($\chi^2(3, N = 80) = 4.46, p = .22$). The premorbid social trajectories comprised 1. good stable (N=45), 2. good, clearly deteriorating (N=19) and 3. poor, slightly improving (N=16). They also did not differ statistically in relation to number of adversities (F(2,77) = 1.460, p = .24). The trajectories are illustrated in figures 8 and 9 and the analyses in table 10.

Global functioning the year prior to treatment entry (GAF function 1 year) decreased with an increasing number of childhood adversities ($r_s(97) = -.22, p = .04$) in the FEP group, while years of education ($r_s(99) = -.07$), occupational status ($r_s(99) = -.06$) and living status ($r_s(98) = .18$) were non-significantly correlated with number of adversities. Similarly, the control group saw no significant correlations between number of adversities and occupational status ($r_s(100) = .06$) and years of education ($r_s(100) = .05$), while none could be calculated for livings status as everyone lived independently. The correlations are presented in tables 7 and 8.
Figure 8. Social premorbid trajectories for the FEP group (N=80).

Figure 9. Academic premorbid trajectories for the FEP group (N=80).
<table>
<thead>
<tr>
<th></th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer support</td>
<td>61 (65.60)</td>
<td>92 (92)</td>
<td>0.06</td>
<td>0.02-0.15</td>
<td>&lt;0.001</td>
<td>31.47</td>
<td>0.12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.04-0.36</td>
<td>&lt;0.001</td>
<td>14.10</td>
</tr>
<tr>
<td>Adult support</td>
<td>47 (51.10)</td>
<td>95 (95)</td>
<td>0.17</td>
<td>0.07-0.41</td>
<td>&lt;0.001</td>
<td>15.60</td>
<td>0.82&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.27-2.52</td>
<td>0.725</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of adversities, mean (SD)</td>
<td>2.87 (1.98)</td>
<td>0.65 (1.13)</td>
<td>2.56</td>
<td>1.91-3.42</td>
<td>&lt;0.001</td>
<td>40.18</td>
<td>2.64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.85-3.76</td>
<td>&lt;0.001</td>
<td>28.48</td>
</tr>
<tr>
<td>Number of adversities, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.30&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.63-3.24</td>
<td>&lt;0.001</td>
<td>22.38</td>
</tr>
</tbody>
</table>

Notes: OR, Odd ratio; CI, confidence interval

<sup>a</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education

<sup>b</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and number of adversities

<sup>c</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and adult support

<sup>d</sup> Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and peer support
**Metacognitive case control comparisons (paper 3)**

Paper 3 sought to compared the FEP group with non-clinical control persons and found that it had poorer metacognitive abilities on the total MAS-A score and the MAS-A subcategories. Self-reflection differed the most (z-score = 5.29, p <0.001) and Awareness of the Mind of the Other differed the least (z-score= 4.37, p <0.001).

**Metacognition and adversity in relation to symptom profiles (paper 3)**

Paper 3 additionally sought to examine how metacognition and childhood adversities affected positive and negative symptoms individually and in conjunction by comparing different symptom profiles. The positive and negative symptom profiling resulted in four clusters. They are illustrated in figure 10. The model that compared the groups on social and academic PAS, DUP, metacognition and number of adversities showed an overall difference between the groups (Pillais’ Trace = .42, F(15, 231) = 2.51, p = .002), which the post-hoc analysis showed was due to differences in the MAS-A total scores (p < 0.001). None of the other variables differed between the symptom groups. The difference in MAS-A was such that both groups with high negative symptom scores had lower MAS-A scores than the group with low positive and negative symptoms. The parallel high positive symptom groups did not differ from the low positive and negative symptoms group. Accordingly, all the MAS-A subscales correlated with negative symptom ratings (r = -0.29 to -0.415) and none of them with positive symptom ratings (r = -0.14 to -0.03). The MANOVA and correlation analyses are presented in tables 11 and 12, respectively. Regarding childhood adversity, there were no significant correlations between the number of childhood adversities and total MAS-A scores.
Figure 10. The distribution of positive and negative symptoms in symptom groups (N=94).

Notes: Cluster groups based on positive and negative symptom z-scores
Table 11. Metacognition and childhood adversity comparisons in groups based on positive and negative symptoms (N=83).

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>F(15, 231)</th>
<th>P=</th>
<th>η²</th>
<th>Post hoc Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized discriminant function coefficients</td>
<td>Low negative/low positive (n=34)</td>
<td>Low negative/high positive (n=14)</td>
<td>High negative/low positive (n=12)</td>
<td>High negative/high positive (n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS-A total</td>
<td>0.96</td>
<td>16.03 (3.19)</td>
<td>14.57 (3.33)</td>
<td>11.71 (3.80)</td>
<td>13.35 (2.99)</td>
<td>6.40</td>
<td>&lt; 0.001</td>
<td>1 &gt; 3, 4; 2 &gt; 3</td>
</tr>
<tr>
<td>DUP</td>
<td>0.54</td>
<td>119.09 (177.06)</td>
<td>179.21 (214.17)</td>
<td>129.92 (248.68)</td>
<td>192.26 (225.54)</td>
<td>2.57</td>
<td>0.06</td>
<td>0.09</td>
</tr>
<tr>
<td>Number of adversities</td>
<td>-0.40</td>
<td>2.88 (1.97)</td>
<td>2.50 (1.61)</td>
<td>2.92 (1.98)</td>
<td>3.04 (1.97)</td>
<td>0.24</td>
<td>0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>Premorbid academic</td>
<td>0.31</td>
<td>2.36 (1.15)</td>
<td>1.61 (1.37)</td>
<td>2.25 (0.98)</td>
<td>2.93 (1.53)</td>
<td>1.38</td>
<td>0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>Premorbid social</td>
<td>-0.44</td>
<td>1.90 (1.28)</td>
<td>2.83 (1.23)</td>
<td>1.78 (1.62)</td>
<td>2.38 (1.45)</td>
<td>1.15</td>
<td>0.35</td>
<td>0.04</td>
</tr>
</tbody>
</table>

a MANOVA comparing metacognitive total score (MAS-A), DUP, number of adversities, premorbid academic and social functioning. Pillai's Trace = .42, F(15, 231) = 2.51, p = .002, Partial Eta Squared = 0.14.

b DUP and premorbid social adjustment were entered as logarithmically transformed variables.

c Including CTQ subcategories with moderate-severe cut-off scores, institutionalization and separation from primary caregivers.
Table 12. Pearson correlation analysis of metacognition and other variables in persons with FEP (N=83)

<table>
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<th>1.</th>
<th>2.</th>
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<th>4.</th>
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<th>8.</th>
<th>9.</th>
<th>10.</th>
<th>11.</th>
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<td>1. MAS sum score</td>
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<td></td>
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<tr>
<td>2. DUP</td>
<td>-.015</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Number of adversities</td>
<td>.139</td>
<td>.240’</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. PAS academic</td>
<td>-.138</td>
<td>-.014</td>
<td>.000</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>5. PAS social mean</td>
<td>.092</td>
<td>.176</td>
<td>-.060</td>
<td>.200</td>
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<td>6. Positive symptoms†</td>
<td>-.113</td>
<td>.352’</td>
<td>.120</td>
<td>.126</td>
<td>.228’</td>
<td>1</td>
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<td>7. Negative symptoms†</td>
<td>-.417”</td>
<td>-.176</td>
<td>-.065</td>
<td>-.014</td>
<td>.050</td>
<td>-.047</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>8. Self-reflectivity</td>
<td>.902”</td>
<td>-.031</td>
<td>.145</td>
<td>-.095</td>
<td>.124</td>
<td>-.094</td>
<td>-.415**</td>
<td>1</td>
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<tr>
<td>9. AoM</td>
<td>.757”</td>
<td>.033</td>
<td>.130</td>
<td>-.220</td>
<td>-.069</td>
<td>-.065</td>
<td>-.327**</td>
<td>.564**</td>
<td>1</td>
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<td>10. Decentration</td>
<td>.776”</td>
<td>.111</td>
<td>.162</td>
<td>-.210</td>
<td>.063</td>
<td>-.025</td>
<td>-.355**</td>
<td>.660**</td>
<td>.701**</td>
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<td>11. Mastery</td>
<td>.828”</td>
<td>-.074</td>
<td>.056</td>
<td>-.028</td>
<td>.122</td>
<td>-.140</td>
<td>-.286**</td>
<td>.650**</td>
<td>.424**</td>
<td>.444**</td>
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</table>

Notes: AoM, awareness of the mind of the other
* p < 0.05, ** p < 0.01
† Positive and negative symptoms as defined by van der Gaag (van der Gaag et al., 2006)

Discussion

The aim of this study was to determine the prevalence of childhood adversity and metacognitive impairments in a representative sample of people with non-affective psychosis and to explore how these factors contributed to outcomes. It found that nine out of ten participants with non-affective psychosis had been exposed to at least one form of serious childhood adversity compared with about a third of the control group (p < 0.01), and that the majority of this subgroup had been exposed to three or more forms of adversity compared to only 7% of the exposed subgroup of control participants (p < 0.01). There were correlations between the various forms of childhood adversity and individual odds ratios for psychosis were greatly diminished by controlling for variance in other forms of adversity. Furthermore, perceived peer support during childhood decreased the risk of psychosis (p < 0.01) and the risk conferred by exposure to childhood adversity. In addition, family contact and global functioning during the year prior to treatment were both negatively correlated with childhood adversity. The only predictor of negative symptoms was impaired metacognition, which was associated with negative symptoms independent of the level of positive symptoms.
Prevalence of childhood adversity in FEP

We sought to determine the prevalence of childhood adversity in people with non-affective FEP and in a matched non-clinical control group whilst avoiding the methodological flaws affecting earlier research. The overall prevalence of all forms of childhood adversity in our study (89%) was higher than in most previous FEP studies, (median = 74%, range: 44–94%; see figure 4). This was as expected, due to the various methodological limitations of the earlier studies, listed in ‘Prevalence and risk of childhood adversities in non-affective psychosis’, including failure to assess certain forms of adversity and use of unvalidated or inappropriate assessment instruments. Also as expected, the prevalence of adversity in our control group was lower than in previous studies as our control group was exclusively non-clinical whereas the control groups in earlier studies included people with psychiatric disorders. Our figures for the prevalence of different types of childhood adversity were higher than in previous studies with respect to physical and emotional abuse and emotional physical neglect, whilst they were similar with respect to sexual abuse and parental death/loss and separation.

We found no difference between the frequency of parental death in the FEP and control groups, which replicates the finding of Aas et al. and the meta-analysis by Varese et al. (Aas et al., 2011; Filippo Varese et al., 2012). Parental loss is usually a random and unintentional event, and thus less likely to be associated with abuse or neglect. If it occurs as an isolated adverse event, in the context of continuing adequate care it may not damage mental development seriously (Anda et al., 2006; Slade, 2005).

A quarter of our FEP group had been institutionalized; one earlier one FEP study reported a frequency of 4.4% (Fisher et al., 2010) and two non-FEP psychosis studies reported frequencies of 35% and 41% (Robins, 1996; Rosenberg et al., 2007). A Danish population study published in 2003 found that 1.1% had been institutionalized or placed in foster care before age 17 years (Egelund, T and Hestbæk, A, 2003), which is about half the rate of institutionalization in our control group. The findings of previous FEP studies are illustrated in figures 4 and 5, whilst ours are presented in Table 6. Our prevalence rates for both FEP group and control group are generally more reliable than those of previous studies because the CTQ is a well-validated and inclusive instrument and we included parental separation and institutionalization.
Form and amount of childhood adversity

It is clear from our study that ‘amount’ of, or overall exposure to adversity is a crucial determinant of the risk of psychosis. This finding is in line with most of the extant literature (Heins et al., 2011; Rubino et al., 2009; Shevlin et al., 2007), however to date only one FEP study has examined the relationship between overall exposure to childhood adversity and risk of psychosis, and no clear dose-response effect was found (Fisher et al., 2010). This may have been due to the inclusion of people with other psychiatric disorders – another population in which exposure to childhood adversity is prevalent - in the control group. Overall, there is now stronger evidence for a dose-response relationship between childhood adversity and risk of psychosis.

We found that the risk of psychosis associated with particular forms of childhood adversity greatly decreased when the analysis controlled for variance in other forms of adversity. We suggest these reductions reflect the frequency with which the various forms of adversity co-occur, and that rather than attempting to assess their impact individually they should be combined for the purposes of risk analysis. In the case of physical abuse, for example, controlling for variance in exposure to other forms of adversity rendered the odds ratio for the increase in risk non-significant. Instead of interpreting this as an indication that physical abuse is not a factor in development of psychosis, as would be usual with logistic regression results of this kind, we propose an alternative explanation.

In our sample, physical abuse always co-occurred with other forms of adversity, with one exception. Several previous studies have found physical abuse to remain a significant predictor after controlling for other forms of adversity, which makes it likely that it was also, in fact, a risk factor for psychosis in our sample. The same logic can be applied to findings relating to other types of childhood adversity in studies which attempted to control for variance in forms of adversity (Daalman et al., 2012; Fisher et al., 2010; Rubino et al., 2009; Shevlin et al., 2007). We suggest they find different childhood adversities to be essential because different groups of people with psychosis have different childhood adversity profiles. For example, two studies using the same assessment instrument reported widely varying rates of exposure to emotional abuse in their FEP samples (70%, Spidel et al., 2010; 11%, Wang et al., 2013). This leads us to suggest that the type of childhood adversity has little impact on the risk of psychosis and that a model that combines them may provide a more accurate estimate of the associated increase in risk.

The dose-response effect we observed suggests that both the severity and persistence of childhood adversity are important determinants of risk, because number of adversities represents more severe
adverse events, both of type and frequency. Our FEP group had definitely experienced ‘severe’ childhood adversity, because we used CTQ cut-off scores that ensured that only severe or extreme adversity was taken into account; parental separation was only counted in cases where it was not due to divorce and the rate of institutionalization - an indication of inadequate caretaking (Andersen, 2008) - was high. We can also state with confidence that our FEP group had experienced persistent childhood adversity; 77% had experienced negative CTQ events often or always, or positive events never or rarely and 34% of the remaining 23% had experienced more than one form of adversity or institutionalization. Institutionalization inevitably indicates ‘persistent’ adversity because cases takes a long time to investigate and instigate (Andersen, 2008) and the average duration of institutionalization was long, i.e. 2.8 years. The evidence that substantial proportions of the FEP group were exposed to severe or persistent abuse raises the question of whether there is a need for instruments, which assess these aspects of adversity more explicitly than do the CTQ and other scales currently available.

That the severity and persistence of childhood adversity are more important determinants of risk of psychosis than the form of adversity is consistent with the trauma literature, which suggests that severity and duration are what separate everyday accidents from traumatizing experiences (Grayson J., 2006; Perry, 2002; Teicher et al., 2003). The trauma literature also stresses the centrality of dysfunction of the organism (Payne et al., 2015), which can result from all seven types of childhood adversities (Grayson J., 2006). This finding also fits well with the majority of childhood adversity-psychosis theories, the first of which makes reference to the core stress response system, the hypothalamic-pituitary-adrenal (HPA) axis (Barker et al., 2015; Myin-Germeys and van Os, 2007; Read et al., 2014). HPA-axis dysregulation has been implicated in functional deficits in people with PTSD, such as memory deficits and stress reactivity. Similarly, the established stress-vulnerability theory of psychosis suggests that people with psychosis are more vulnerable than others to stressful life events (Zubin and Spring, 1977). Recently, researchers have linked this vulnerability, which has most often been considered to be caused by genetic variants, to childhood adversity and argued that the HPA-axis mediates the relationship between childhood adversity and vulnerability to psychosis (Barker et al., 2015; Myin-Germeys and van Os, 2007; Read et al., 2014). Trauma researchers have argued that traumatized children may shift to an abnormal developmental trajectory, and that this is mediated by changes in the HPA-axis (Teicher et al., 2003). There is evidence that the HPA-axis is both hyper-reactive and perturbed in people with non-affective psychosis. The HPA-axis is most easily studied by measuring cortisol levels. A meta-analysis of
people with FEP concluded that they had higher baseline activation of the HPA axis, i.e. higher baseline cortisol levels, and a reduced response to acute stress compared with non-clinical controls (Borges et al., 2013).

A meta-analysis of mixed psychosis samples concluded that in comparison with non-clinical controls they had lower cortisol levels both whilst anticipating a social stressor and during exposure to that stressor (Ciufolini et al., 2014). In people with psychosis baseline HPA-axis activity seems to be higher and the stress response lower. This has been linked to childhood adversity on the grounds that children and adults exposed to childhood abuse or neglect also have altered HPA-axis function. One large study found that young children exposed to adversity had lower, more stable cortisol levels throughout the day (Bernard et al., 2010). A smaller study of 117 abused and neglected three-to-six year-olds found that they had lower morning cortisol levels than non-abused peers (Bruce et al., 2009). A review of studies of young children reported that 27 of 30 studies had found that broadly defined childhood adversity affected baseline cortisol levels or the cortisol stress response, and that in 13 of these studies the stress response was increased (Hunter et al., 2011); however the authors were unable to carry out meta-analysis due to the heterogeneity of the studies, mainly with respect to measurement regimes.

Some of the studies showed that age influenced the stress response and it seemed that HPA axis activity changed over time. A study of adult women with or without depression or anxiety found that those who also had a history of child abuse had greater cortisol stress responses than control participants (Heim et al., 2000). A small study (N=14) which directly compared people with non-affective psychosis who had or had not experienced childhood adversity (assessed with the CTQ) found an association between childhood adversity and lower waking cortisol levels (Braehler et al., 2005).

In summary, it is clear that childhood adversity is associated with altered HPA axis functioning in both children and adults and that the HPA-axis is altered in people with non-affective psychosis. However, it seems that the HPA-axis changes over time and further research is needed to determine the exact mechanism of any pathogenic relationship.

Alongside the cortisol response there is a mesolimbic dopamine response to stress (Brunelin et al., 2008; Howes and Murray, 2014; Wand et al., 2007). Although it has not been as thoroughly studied in relation to childhood adversity, two studies showed an exaggerated response in people who had little parental care (Pruessner et al., 2004; Soliman et al., 2008). People with non-affective
psychosis have also been shown to have a greater dopamine response to metabolic stressors than their siblings or a control group (Brunelin et al., 2008) and there is a positive association between dopamine deregulation and psychotic symptoms in people with psychosis (Howes and Murray, 2014). Some researchers have suggested that the HPA-axis mediates the relationship between childhood adversity and psychosis via the dopamine system (Barker et al., 2015; Belvederi Murri et al., 2012). Others suggest that the dopamine system is disrupted by childhood adversity and thus directly implicated in the generation of positive symptoms (Howes and Murray, 2014).

Observations of HPA-axis dysfunction and dopamine deregulation are consistent with the notion of a dose-response relationship between childhood adversity and risk of psychosis; more severe, persistent or frequent exposure would be expected to cause greater dysfunction and thus increase the risk of psychosis. The HPA-axis and mesolimbic dopamine system might also represent the dysfunctional circuits posited by Somatic Experiencing trauma theory. A mechanism based on dysfunction of the dopamine system or HPA system would also be consistent with the suggestion that type of adversity is relatively unimportant, since all types of adversity cause a hormonal stress response (Braehler et al., 2005; Bruce et al., 2009; Hunter et al., 2011). Researchers should consider examining whether firstly, there is a dose-response relationship between childhood adversity and dysfunction of the HPA and dopamine systems and secondly, whether dysfunction of these systems is related to risk of psychosis.

Social defeat theory, which proposes that ongoing experiences of social defeat or exclusion may cause psychosis by sensitizing the dopamine system (Selten et al., 2013; Selten and Cantor-Graae, 2005; van Os et al., 2000), provides the basis for a second mechanism linking childhood adversity and psychosis. There is evidence of dopamine sensitization to social defeat in animals, but only the two studies of low maternal care mentioned above have investigated - and found - a similar relationship in humans (Pruessner et al., 2004; Soliman et al., 2008). It has been suggested that childhood adversity is one of the causes of social defeat because all intentional abuse and neglect, including peer bullying - which also increases the risk of psychosis (Filippo Varese et al., 2012) - involve exclusion from a social relationship. The type of adversity is relevant here in the sense that the adversity must be perceived as exclusion, but it is not relevant for the distinction between the seven types of adversity in this study. The social defeat theory explains why parental death and other forms of severe but accidental childhood adversity may not increase the risk of psychosis (Selten et al., 2013) and it is consistent with a dose-response effect as it states that the adversity must be long-term. Another possible mechanism by which social defeat could lead to
psychosis is by causing the development of negative schemata about oneself and others, thus increasing external attention and attribution and result in the hearing of voices and paranoia (Birchwood et al., 2000b). This account also places the emphasis on the quantity and severity of childhood adversity rather than the specific form it takes.

The last theory in support of our conceptualization is dissociation, which is defined as the splitting of functions of the self which are normally integrated; including consciousness and identity (American Psychiatric Association, 2013; World Health Organization, 2007). It is widely acknowledged that dissociation occurs in response to trauma and dissociation is most often understood as a mechanism which shields individuals from unbearable suffering (Longden et al., 2012). In the context of psychosis it has mainly been explored in relation to hallucinations, which are thereby “understood as disowned components of the self (or self– other relationships)” (Longden et al., 2012). A recent meta-analysis concluded that there is a robust relationship between the hearing of voices and dissociative symptoms and that dissociation may mediate the relationship between trauma and voice hearing (Pilton et al., 2015). Dissociation is usually considered to arise in response to an overwhelming event but recently, owing to evidence demonstrating that it is strongly associated with emotional neglect, it has been suggested that it may constitute an adaptive response to persistent neglect (Schalinski and Teicher, 2015). Again, given that several types of childhood adversity can be considered overwhelming, they should all have the potential to cause dissociation.

In fact, several studies of non-affective psychosis have demonstrated associations between various forms of adversity and dissociation. One non-affective psychosis study reported that dissociation was strongly associated with emotional neglect but less strongly associated with emotional parental and peer abuse, physical neglect and sexual abuse, in an analysis which controlled for covariance in the forms of adversity (Schalinski and Teicher, 2015). Another non-affective psychosis study found that sexual abuse but not physical abuse, emotional abuse or neglect, was correlated with dissociative symptoms and that dissociative symptoms mediated the relation between trauma and hallucination-proneness (F. Varese et al., 2012). A larger study comparing people with FEP and long-term psychosis with a non-clinical control group found that in all three groups childhood adversity was associated with dissociative symptoms and that emotional abuse was the form of childhood adversity most strongly correlated with dissociation (Braehler et al., 2013). A small study of women with long-term non-affective psychosis found that emotional abuse and physical neglect were correlated with dissociative symptoms but that sexual abuse, physical abuse and emotional neglect were not (Schäfer et al., 2006). A general population study (Teicher et al., 2006) showed
that verbal aggression and having witnessed violence were better predictors of dissociation than sexual and physical abuse. In summary, dissociation and - hence the development of psychotic symptoms - seem to be influenced primarily by factors other than type of adversity. The severity and frequency of adversity do seem to be important; Schalinski et al. (2015) and Teicher et al. (2006) demonstrated a positive association between the severity of dissociative response and the amount of adversity an individual had experienced.

In summary, we have tried to develop a model that accounts for the full range of findings from our own and others’ research. This model proposes that factors common to traumatization and experience of childhood adversity, such as the circumstances and physical and mental responses are more important than type of adversity in determining risk of psychosis. The above-mentioned theories have provided some of the possible mechanisms that may represent these common factors.

**Childhood adversity as a causal factor**

Our results provide corroboration for a causal relationship between childhood adversity and psychosis in several ways. First, we demonstrated a dose-response relationship, thus meeting the gradient criterion proposed by Hill et al. (1965). Second, we confirmed that childhood adversity meets the temporality criterion: 89% of those who reported trauma in the Brief Betrayal Trauma Survey interview reported that it had happened before the onset of psychotic symptoms. This is in line with the one previous FEP study to examine the issue, which reported that 98% of the sample had experienced physical and/or sexual abuse before onset of psychosis (Conus et al., 2010). Lastly, the lack of a gene-environment interaction between incidence of psychiatric disorder in the first-degree relatives of index participants and their exposure to childhood adversity suggests that risk due to childhood adversity is not dependent of genetic vulnerability.

**Perceived support (paper 2)**

We found that the presence of perceived support during childhood decreased the risk of developing psychosis and that peer support reduced the increment in risk due to childhood adversity.

Roughly, half of those with FEP (49%) had not had peer support (peers in whom they could confide) compared with only 5% of the control group. In other words, absence of peer support increased the risk of developing psychosis 17 times, reduced to a significant 8.5 times after controlling for variance in exposure to childhood adversity. The corresponding numbers for absence of adult perceived support were 34% for the FEP group and 8% for the control group. This suggests
that the risk of developing psychosis increases by a factor of six in the absence of adult perceived support. The risk associated with lack of adult perceived support was, however, eliminated by controlling for variance in exposure to childhood adversity, suggesting either conceptual overlap or simple co-occurrence of both factors. Adult support and number of forms of adversity were moderately correlated ($r_{s}(93) = -0.44, p < 0.01$); emotional neglect was the CTQ adversity category most strongly correlated with lack of adult support ($r_{s}(93) = -0.48, p < .01$). Emotional neglect was the only CTQ category containing an item that directly tapped psychological support, namely “My family was a source of strength and support” so this makes sense; however given that this item is one of 25, the maximum potential conceptual overlap is only $1/25^{th}$ of the CTQ. We therefore suggest that co-occurrence is the more likely explanation, since the majority of forms of adversity assessed occur in the home (Trauelsen et al., 2015) and a recent qualitative study of our sample suggested that it can be hard to find support in an environment where abuse or neglect occur (Jansen et al., Under review).

Peer support, but not adult support, reduced the effect that childhood adversity had on the risk of developing psychosis, suggesting that it may be a resilience factor. There were no interactions between support and number of forms of childhood adversity to which an individual was exposed, and hence no support for the notion that the severity of adversity influenced the impact of support on risk of developing psychosis or vice versa. No other psychosis studies have examined perceived support in childhood, but a population study found that having small primary support groups predicted the presence of psychotic symptoms 18 months later, even when controlling for variance in exposure to adversity (Wiles et al., 2006).

We found that childhood adversity was negatively correlated with current face-to-face family contact, but not phone contact, indicating that childhood adversity may have an enduring impact on family relationships. This is presumably because the family continues to be a source of adversity or because earlier adversity has not been managed effectively and hence it is difficult for the affected person to see his or her family. Some of the participants in our FEP sample found it very uncomfortable to be with their family (Jansen et al., Under review). The move to use family intervention in cases of FEP is a recognition that a critical, emotionally over-involved and hostile family environment (Expressed Emotion) is predictive of relapse (Butzlaff and Butzlaff, 1998).
Premorbid and present functioning (paper 2)

Contrary to our prediction, our results suggest that childhood adversity is not associated with a poorer premorbid trajectory. Although such a connection would make sense and is supported by findings from the general population and a few recent psychosis studies (Conus et al., 2010; Schenkel et al., 2005; Stain et al., 2014), our results provided little evidence that it exists. The only similar published study found that childhood adversity was unrelated to changes in premorbid adjustment during the transition from childhood to late adolescence (Stain et al., 2014). Change disregards age of psychosis onset and may therefore include subjects who already have psychotic symptoms. Taken together the evidence suggests that there is no – or no simple – relationship between childhood adversity and premorbid adjustment trajectories.

The neurodevelopmental account of how premorbid adjustment relates to non-affective psychosis is more widely accepted. This proposes that premorbid deterioration reflects a deterioration in brain functioning which is caused by genetic or biological factors. We therefore examined whether incidence of psychiatric illness among first degree relative was related to trajectory and found that it was not related to premorbid social ($\chi^2(2, N = 70) = 2.81, p = .25$) or academic ($\chi^2(3, N = 69) = 1.83, p = .61$) trajectories. In summary, our results point towards the absence of a relationship, or a complicated relationship, between childhood adversity, familial risk and premorbid trajectories.

Termination of adversity followed by functional recovery could account for the lack of association between childhood adversity and premorbid trajectories. A trauma study found that children’s IQ increases dramatically when they are removed from an abusive or neglectful environment to a safe and caring one (Perry, 2002, p. 91) and, as mentioned in our discussion of causality, Kellerher et al. showed that psychotic symptoms tended to diminish when physical and emotional abuse ended (Kelleher et al., 2013). It is possible that brain development catches up or follows a more functional course when the child’s environment improves (Teicher et al., 2003) or that our sample improved their coping or that the environment recognized and improved upon academic or social problems. In summary, it would be useful to study premorbid trajectories prospectively.

The hypothesis that the breadth of exposure to childhood adversity would be related to lower global functioning was confirmed. Premorbid adjustment was assessed with reference to the period prior to onset of the first psychotic symptoms, which occurred at 17 years on average, whereas global functioning was assessed over the year before treatment started, which occurred at 22 years on average. The difference in the relationship between childhood adversity and premorbid adjustment
or global functioning suggests that childhood adversity may only have begun to affect functioning in our FEP participants at the point where their symptoms were becoming evident. However, the correlation between global functioning and adversities was not very strong, and given the relative lack of other studies and the inconsistency in their findings (Addington et al., 2013; Duhig et al., 2015; Gil et al., 2009; Lysaker et al., 2001), this result will have to be confirmed in future FEP studies.

Contrary to our hypotheses, we did not find a relationship between childhood adversity and years of education, living environment or occupational status. Two other studies reported similarly negative findings with respect to occupational status (Campbell et al. 2013; Duhig et al., 2015), although Spence et al. (2006) found a positive association between childhood adversity and occupational status and Conus et al. (2010) a negative one. Conus et al.’s finding was supported by a study of participants at ultra high risk of psychosis (Yung et al., 2015), which showed that participants who had experienced childhood adversity had lower occupational status at follow-up. The heterogeneity of findings in this area may be partly accounted for by methodological factors. One study based adversity assessments on a file audit and only included physical and sexual abuse (Conus et al., 2010). This means that a larger proportion of their group than reported may have experienced childhood adversity thus confounding the results. One study was a non-FEP study of people with an average age of 43 years who had received a mean 15 years of psychosis intervention. Such a group is very different from a FEP group, particularly with respect to the potential for changes caused by interventions, making comparison difficult.

Living environment was also unrelated to the number of childhood adversities, but we found that it was related to institutionalization \( (r_{(95)} = .35, p < .01) \). People who are institutionalized when they reach the age of 18 can ask to remain in similar housing until they turn 23, which is a possible confounding factor in this analysis. The lack of association between childhood adversity and years of education may also have been a consequence of Danish social policy; the Danish school system is very egalitarian and provides a lot of support to children who require it (“Education Policy Outlook Highlights: Denmark - OECD,” n.d., p. 6; 16). The relationships between childhood adversity and education, living environment and occupational status require further examination, preferably in prospective studies.
Metacognitive case control comparisons (paper 3)

As hypothesized, the FEP group had lower metacognitive abilities than the control group. This is in line with the ToM literature (Bora and Pantelis, 2013; Smeets-Janssen et al., 2013) and the one metacognitive case-control study (Rabin et al., 2014). The metacognitive levels in our study correspond closely with those reported in the biggest FEP study (McLeod et al., 2014) although on some subscales they are higher than those reported in two FEP studies whose small samples (N = 34 and N = 26) may have made them unrepresentative (Macbeth et al., 2014; Vohs et al., 2014). The levels in the control group correspond closely with those in another control group from a Danish depression study (Ladegaard et al., 2014).

Metacognition and adversity in relation to symptom profiles (paper 3)

As expected metacognitive abilities were negatively associated with negative symptoms and we were unable to detect an independent association with positive symptoms. These results suggest that previously found associations between metacognitive abilities and positive symptoms might have been confounded by negative symptoms, something which might also explain the inconsistency of findings in this area (Hamm et al., 2012; Lysaker et al., 2005; Macbeth et al., 2014; McLeod et al., 2014; Nicolò et al., 2012). Future research should take negative symptoms into account when exploring the relationship between metacognition and positive symptoms, but our results suggest that investigation of the relationship with negative symptoms is more important.

The negative symptom component that we used (van der Gaag 2006) includes blunted affect, emotional withdrawal, poor rapport, apathetic social withdrawal, lack of spontaneity, motor retardation and uncooperativeness. These symptoms can be understood in very many different ways, such as part of anxious or depressive symptoms, coping strategies, attachment problems or cognitive deficits. When exploring negative symptoms in relation to metacognition, they are considered psychological phenomena. Suggestions for the relation include that reduced understanding of self causes poor rapport through difficulties with expressing oneself and that reduced understanding of self and others cause a poor understanding of one’s experiences and thereby purposelessness (Lysaker et al., 2015), which may be conveyed as lack of spontaneity and volition in addition to withdrawal. Metacognitive deficits may also cause negative symptoms by decreasing the ability to comprehend situations, causing complex social situations to be avoided. However, to answer these hypotheses, the negative symptoms will have to be studied one by one.
Most previous FEP studies have found weak or no correlations between total adversity scores and positive and negative symptoms (Duhig et al., 2015; Fisher et al., 2010; Ramsay et al., 2011), but a few have found that total adversity scores were related to positive and not negative symptoms (Ucok A. and Bikmaz S., 2007). However, a recent meta-analysis concluded that childhood adversities increased the risk of perseverance of psychotic experiences in both clinical and non-clinical populations (Trotta et al., 2015). It is possible that especially positive symptoms in the first acute phase of a psychosis enters a sort of vicious cycle, or is influenced by numerous factors, which disturbs patterns of associations in other phases. However, these questions require further examination. There was no relationship between childhood adversity and metacognition or symptoms, implying that childhood adversity is not a predictor of symptom severity in people with FEP and that any effect on metacognition is weak or overshadowed by factors that are more important. As this is the first study to assess metacognition and the various forms of childhood adversity comprehensively the results must be replicated.

**Study strengths and limitations**

A retrospective, cross-sectional study can only be used to uncover associations, not as the basis for a strong claim about causality. This is especially relevant to claims about the relationship between childhood adversity and psychiatric disorders. There has been strong criticism of the reliance on recollection in assessments of exposure to childhood adversity, particularly in the case of people with non-affective psychosis as their perception of reality may be distorted; however, the more specific criticism has been refuted by studies showing that psychiatric status has no influence on reports of childhood adversity.

One FEP study found that psychotic symptom severity was not associated with CTQ scores (Fisher et al., 2011) and a population study found no association between childhood adversity and reported abuse or general psychopathology (Fergusson et al., 2000). The CTQ has proved reliable in psychosis populations, with good test-retest reliability over four weeks (Kim et al., 2013) and reasonable test-retest reliability over seven years (Fisher et al., 2011). The minor lack of concordance over the longer interval was due to failure to confirm initial reports of adversity rather than to low specificity (Fisher et al., 2011). Similarly, Fergusson et al. (2000) and a reliability review concluded that people were likely to under-report but not to make false claims of childhood adversity (Hardt and Rutter, 2004). A similar pattern of under-reporting and an absence of false claims was also found in mothers with non-affective psychosis who were asked to recall obstetric
complications (Buka et al., 2000). In conclusion, these findings suggest that there probably are some recall bias, but that they will consist mainly of false negatives and be equally prevalent in FEP and control groups. Any under-reporting will have confounded analyses involving childhood adversity regardless of whether an association was demonstrated or not.

The cross-sectional design also has implications for the analyses of effects involving metacognition, in particular because negative symptoms such as decreased initiative and poverty of speech may have reduced the amount of information obtained in the semi-structured IPII interviews. This might inflate the association between MAS-A and negative symptoms; however there is strong evidence on the direction of the relationship from a longitudinal study showing that baseline MAS-A predicted future negative systems when controlling for variance in baseline negative symptoms (McLeod et al., 2014). The metacognitive data may also have been affected by the use of un-blinded assessment, probably in the form of a bias towards lower scores in the FEP group. The scores in our study were nonetheless in line with those in other studies in both the cases and controls, and both assessors had been trained by the Lysaker research group and had excellent inter-rater reliability.

The study design did not allow for early adversity assessment, as adults usually cannot remember the first 3-4 years of life. This may have influenced the psychosis risk estimates and the lack of associations between childhood adversities and metacognitive abilities.

The Danish Health Service is extensive and is thought to register almost all new cases of FEP. Despite a dropout rate of 48% we consider the study representative. The higher rates of paranoid psychosis (11%), unspecified psychosis (10%) and acute psychosis (9%) in the excluded group were probably caused by the difference in assessment method for the FEP groups; OPCRIT was only rarely used in the clinical setting. The prevalence of exposure to childhood adversity is assumed to be similar in paranoid and unspecified psychoses and schizophrenia and may be higher in cases of acute psychosis (Myin-Germeys and van Os, 2007). The lower incidence of childhood adversity in the included and analyzed subgroups may have been due to the smaller proportion of women in these groups, given that there is evidence from psychosis studies that girls experience more childhood adversity than boys (Fisher et al., 2009). Matching by parental education has strengthened our findings by reducing confounding by social factors other than childhood adversity. Additional issues relevant to specific analyses are discussed in the relevant papers. Sample size and reliability were satisfactory in all analyses. The CTQ satisfies the proposed criteria for assessment instruments in that it uses straightforward, evaluation-free questions and assesses subcategories with
multiple questions (Hardt and Rutter, 2004).

**Clinical implications**

The high prevalence of severe childhood adversity in people with FEP has societal and clinical implications. Societal initiatives should aim to reduce child abuse and neglect or ensure its early detection by i. educating society in general and influential professionals, such as medical health professionals, pedagogues and teachers in particular; ii. making it easier for children to seek help and protect themselves and iii. improving management of perpetrators (Longden, 2012). Our finding that a perceived lack of support is common among people with FEP implies that it would be helpful to provide social support for children who are without it. In addition, information campaigns to educate the public about the risk factors for psychosis might reduce the stigmatization of people with psychosis by promoting the view that they are not innately different; rather they may have been exposed to extreme life circumstances. Service user communities are fighting to disseminate this view (McCarthy-Jones, 2013) and they encourage clinicians to ask their users what has happened to them instead of what is wrong with them (“Silje Marie Strandberg | ISPS NY 2015,” n.d.).

Focusing on the prevalence of childhood adversity might also promote a recovery-oriented approach to management (Zipursky and Agid, 2015), as it is considered possible to recover from the consequences of adversity. This is also important on a clinical level. Family-intervention and psychoeducation for users and relatives may enhance recovery by enabling them to understand how childhood adversity can affect psychological, emotional and physiological functioning. The prevalence of childhood adversity also provides support for a policy of incorporating individual psychotherapy into existing intervention plans, because childhood adversity is theoretically amenable to psychotherapy and there is evidence that individual therapy is more effective than group therapy for people with PTSD caused by childhood adversity (Ehren et al., 2014).

Use of psychotherapy is also supported by a recent review which concluded that psychotherapy for people with PTSD can ameliorate HPA-axis dysregulation (Jones and Moller, 2011). A review concluded that trauma-focused therapy was more effective for the treatment of PTSD than non-trauma-focused therapy (Ehren et al., 2014), so it may be that it should be the preferred choice. Trauma-focused therapy is already underway. TRauma-Informed Psychotherapy for Psychosis (TRIPP) is an intervention that uses shared formulation in its aim to create safety and deal with trauma symptoms (Bendall, S, 2014). PTSD interventions are also being tested in psychosis
populations; they appear to be safe and effective (Frueh et al., 2009; van den Berg et al., 2015). Our finding of low metacognitive abilities in the FEP group supports the general implementation of psychotherapy because metacognitive improvement is considered a crucial outcome for effective psychotherapy (Fonagy and Allison, 2014). Positive and negative symptoms strongly predict current and future social and vocational functioning (Blanchard et al., 2011, 2005; Jordan et al., 2014; Kirkpatrick et al., 2006). Especially negative symptoms are still largely unaffected by pharmacological and psychosocial interventions (Wykes et al., 2008). Metacognitive abilities are being targeted in non-affective psychosis intervention studies (Hillis et al., 2014; Peyroux and Franck, 2014). These direct metacognitive approaches may improve the negative symptoms, as their connection seem so strong. Social relational difficulties, which are widespread among people with FEP, may also be improved by psychotherapy since interpersonal attachment and metacognition are the focal points of the integrative, recovery-oriented therapies which some consider to be the future of psychosis psychotherapy (Hamm et al., 2013).

On a different clinical level, the co-occurrence of several forms of childhood adversity and their prevalence in people with FEP reinforces the need for comprehensive assessments of adversity in psychosis populations. Evidence that the type of adversity appears less important for the risk of psychosis also suggests that interpersonal adversity, which is not assessed by the standard instruments, may play a role in the development of psychosis. When asked about other forms of trauma not mentioned explicitly in the assessment, our FEP group mentioned substance abuse, violence at home, physical illness, early hospitalizations, parental illness and peer bullying. Of these only bullying has been studied systematically in relation to psychosis risk; it increases the risk of psychosis as much as other forms of adversity (Filippo Varese et al., 2012). It is important to recognize that several types of interpersonal adversity may play a role in the development of psychosis; this should be explained to service users and relatives and taken account of in treatment plans, which should thus respect the personal life history of the person with FEP. Our findings also suggest that severity and persistence should be assessed and their possible importance explained.

**Research implications**

The findings of this study have some implications for research in the field. The high level of co-occurrence of the various forms of childhood adversity renders the study of specific forms of childhood adversity difficult and susceptible to confounds; such studies should therefore aim for comprehensive childhood adversity assessment. Our study suggests that investigating other factors
common to trauma and psychosis may be a useful way of uncovering the mechanism underlying the association between the two. HPA-axis dysfunction, experience of social defeat and dissociation are candidate common factors mentioned in the childhood trauma literature. They might include emotional processing, which has been shown to mediate the relationship between childhood adversity and psychotic symptoms (Kramer et al., 2012), other psychological defensive mechanisms and physiological dysfunctions.

Furthermore, future research should explore severity and persistence more explicitly. This could be aided by extending existing assessment tools to include assessment of the periods of adverse events and their frequency. Severity assessment will be difficult to assess, before the mechanisms are better known, though some grading has been usefully applied in different populations, such as the amount of physical injury for physical abuse and the degree of invasiveness for sexual abuse (Evans et al., 2013). The study findings also suggest that involvement of caregivers is an important aspect that should be explored more explicitly. In addition to assessing it, it may be explored in relation to attachment mechanisms as neglect and abuse are attachment traumas that often cause insecure and/or disorganized attachment styles (Jon G. Allen, 2012, p. 46) and since up to 75% of people with FEP have been found to have insecure and/or disorganized attachment behaviour (MacBeth et al., 2011).

Our findings also suggest that caregiver involvement is an important aspect of FEP interventions that should be explored more explicitly. In particular it would be interesting to explore the relationship between caregiver involvement and attachment mechanisms, given that neglect and abuse are attachment traumas that often cause insecure and/or disorganised attachment styles (Jon G. Allen, 2012, p. 46) and that in one study 75% of people with FEP were found to show insecure and/or disorganised attachment behaviour (MacBeth et al., 2011). Age at traumatization may be another important aspect of traumatization as events during certain developmental periods may be more likely to cause psychosis than events in others. Age influences the psychological tools a child has at his or her disposal and hence his or her responses to adversity; similarly the direct neural consequences of an adverse event are dependent on the age of the child (Pietrek et al., 2013). Few studies have been concerned with adversities in the first 3-4 years of life in children with later psychosis though one study is in progress (“The Danish High Risk and Resilience Study - VIA 7,” n.d.). Due to the differential brain development throughout childhood, it may be worthwhile studying these early adversities. Perceived support and adversities during childhood might benefit
from being studied prospectively as more details and thus mechanisms and effects of childhood resilience and adversity on psychosis or positive and negative symptoms may be identified.

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New Directions in Child Abuse and Neglect Research, n.d.


Spence, W., Mulholland, C., Lynch, G., McHugh, S., Dempster, M., Shannon, C., 2006. Rates of childhood trauma in a sample of patients with schizophrenia as compared with a sample of


Appendices

Appendix 1
Search string for risk factors:
(((psychosis OR schizophrenia)) AND ("childhood trauma" OR "childhood adversity")) AND ("2010/01/01"[Date - Publication] : "2015/01/01"[Date - Publication]))
For every decade since 1960.

Appendix 2
Search strings for Psycinfo, Medline, Embase. Search strings were reviewed by research librarian Trine Pontoppidan Kæstel.

Embase
1. psychotrauma/di, dm, ep, et, pc, rh, th [Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Rehabilitation, Therapy]
2. *risk factor/
3. *posttraumatic stress disorder/co, di, dm, ep, et, pc, rh, th [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Rehabilitation, Therapy]
4. psychotrauma/co, di, dm, ep, et, pc, rh, th [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Rehabilitation, Therapy]
5. child sexual abuse/
6. sexual abuse/
7. child abuse/co, di, dm, ep, et, pc, rh, th [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Rehabilitation, Therapy]
8. emotional abuse.mp.
9. domestic violence/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. FEP.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. (early onset psycho* or early onset schizo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. (first episode psycho* or first episode schizo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. (early psychosis or early psychoses or early schizo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. (primary psychosis or primary psychoses or primary schizo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
16. (initial psychosis or initial psychoses or initial schizo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17. 11 or 12 or 13 or 14 or 15 or 16
18. 10 and 17

Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1948 to Present
1. FEP.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. (early onset psycho* or early onset schizo*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. (first episode psycho* or first episode schizo*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. (early psychosis or early psychoses or early schizo*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. (primary psychosis or primary psychoses or primary schizo*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. (initial psychosis or initial psychoses or initial schizo*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. 1 or 2 or 3 or 4 or 5 or 6
8. *Stress, Psychological/di, et, hi, nu, pa, ph, pp, pc, px [Diagnosis, Etiology, History, Nursing, Pathology, Physiology, Physiopathology, Prevention & Control, Psychology]
9. *Stress Disorders, Post-Traumatic/di, ep, et, hi, nu, pa, pp, pc, px [Diagnosis, Epidemiology, Etiology, History, Nursing, Pathology, Physiopathology, Prevention & Control, Psychology]
10. *Risk Factors/
11. "Wounds and Injuries"/px [Psychology]
12. *Child Abuse/co, di, et, hi, nu, pa, pp, pc, px [Complications, Diagnosis, Etiology, History, Nursing, Pathology, Physiopathology, Prevention & Control, Psychology]
13. *Sex Offenses/cl, ep, hi, pc, px [Classification, Epidemiology, History, Prevention & Control, Psychology]
16. *Life Change Events/
17. *Stress Disorders, Traumatic/co, di, ep, et, hi, nu, pa, pp, pc, px, th [Complications, Diagnosis, Epidemiology, Etiology, History, Nursing, Pathology, Physiopathology, Prevention & Control, Psychology, Therapy]
18. *Stress Disorders, Traumatic, Acute/co, di, ep, et, nu, pp, pc, px, rh, th [Complications, Diagnosis, Epidemiology, Etiology, Nursing, Physiopathology, Prevention & Control, Psychology, Rehabilitation, Therapy]
19. *Shock, Traumatic/cl, co, di, ep, et, hi, nu, pa, pp, pc, px, th [Classification, Complications, Diagnosis, Epidemiology, Etiology, History, Nursing, Pathology, Physiopathology, Prevention & Control, Psychology, Therapy]
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 7 and 20

PsycInfo
1. *risk factor/
2. *emotional trauma/
3. *trauma/
4. *posttraumatic stress disorder/
5. *sexual abuse/
6. *physical abuse/
7. *child abuse/
8. *emotional abuse/
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. FEP.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11. (early onset psycho* or early onset schizo*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
12. (first episode psycho* or first episode schizo*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13. (early psychosis or early psychoses or early schizo*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
14. (primary psychosis or primary psychoses or primary schizo*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
15. (initial psychosis or initial psychoses or initial schizo*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16. 10 or 11 or 12 or 13 or 14 or 15
17. 1 or 9
18. 16 and 17
Articles and letter

Article 1 and the letter have been published in Schizophrenia Research. Articles 2 and 3 are under review in peer-reviewed journals.
Paper 1

Childhood adversity specificity and dose-response effect in non-affective first-episode psychosis

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\textsuperscript{d} Centre for Youth Mental Health, the University of Melbourne, Australia
\textsuperscript{e} Orygen: The National Centre of Excellence in Youth Mental Health, Australia
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\textsuperscript{22} Financial support. The study was supported by The Regional Health and Research Foundation, Zealand (AMT Grant number 12-000095); and The Lundbeck Foundation (AMT Grant number R93-A8804).

\textsuperscript{222} This paper is part of the OPUS Zealand research project: Family Intervention in First-episode Psychosis. An investigation of metacognition, expressed emotion and caregiver experiences. From January 1. 2012 the project has the following research group: Erik Simonsen, MD, PhD (PI). Ulrik Haahr, MD (PI). Christopher Hoeier Trier, MSc in Psychology. Marlene Buch Pedersen, MSc in Psychology. Hanne-Grethe Lyse Nielsen, RN. Mette Sjoestroem Petersen, MA (ed) in Educational Psychology, Jens Einar Jansen, PhD. Ulf Soegaard, MD. Anne Marie Trauelsen, MD. From September 1. 2014 Signe Dunker Svendsen, RN. From Psychiatric Research Unit, Psychiatry Region Zealand, Denmark. Early Psychosis Intervention Center, Psychiatry East Region Zealand, Denmark.
ABSTRACT

Background. Reviews conclude that childhood and adolescence sexual, physical, emotional abuse and emotional and physical neglect are all risk factors for psychosis. However, studies suggest only some adversities are associated with psychosis. Dose-response effects of several adversities on risk of psychosis have not been consistently found. The current study aimed to explore adversity specificity and dose-response effects of adversities on risk of psychosis.

Method. Participants were 101 persons with first-episode psychosis (FEP) diagnosed with ICD-10 F20 – F29 (except F21) and 101 non-clinical control persons matched by gender, age and parents’ socio-economic status. Assessment included the Childhood Trauma Questionnaire and parts of the Childhood Experience of Care and Abuse Questionnaire.

Results. Eighty-nine percent of the FEP group reported one or more adversities compared to 37 % of the control group. Childhood and adolescent sexual, physical, emotional abuse, and physical and emotional neglect, separation and institutionalization were about four to 17 times higher for the FEP group (all p<0.01). The risk of psychosis increased two and a half times for each additional adversity. All associations between specific adversities and psychosis decreased when they were adjusted for other adversities.

Conclusion. Our findings suggest that there is a large shared effect of adversities on the risk of psychosis. Contrary to the call for further research into specific adversities, we suggest a search for mechanisms in the shared effects of traumatization. Clinical implications are thorough assessment of adversities and their possible effects.

Keywords: case control; psychological trauma; abuse; neglect; risk
1. Introduction

Childhood and adolescence adversities are now considered risk factors for psychosis (Bonoldi et al., 2013; Matheson et al., 2012; M. van Nierop et al., 2014; Filippo Varese et al., 2012). However, some researchers advise they might be indicators or proxies of social and environmental causal factors (Cutajar et al., 2010; Murray et al., 2013), while others hold that they themselves are causal (Carr et al., 2013; Filippo Varese et al., 2012). Some even suggest that only few adversities increase the risk of psychosis (Fisher et al., 2010).

Prospective and case-control studies have found associations between psychosis and different childhood and adolescent adversities. These include sexual abuse (Cutajar et al., 2010; Elklit and Shevlin, 2011; Fennig et al., 2005; McCabe et al., 2012; F. Varese et al., 2012); emotional abuse (McCabe et al., 2012; F. Varese et al., 2012; Whitfield et al., 2005); physical abuse (Aas et al., 2011; McCabe et al., 2012; F. Varese et al., 2012; Whitfield et al., 2005); parental loss/separation (Aas et al., 2011; Agid et al., 1999); and emotional and physical neglect (McCabe et al., 2012; F. Varese et al., 2012). Several of these studies found that the risk of psychosis was associated with some but not other adversities (Aas et al., 2011; McCabe et al., 2012). There is no clear pattern of particular adversities increasing the risk of psychosis. Moreover, in these studies, the adversities in question were not adjusted for other adversities, making it impossible to draw conclusions about whether specific adversities confer a greater risk of psychosis.

Several studies, however, have adjusted for other adversities. They find different adversities to be central for risk of psychosis: physical abuse from the mother (Fisher et al., 2010); physical abuse and violence at home (Shevlin et al., 2007); physical abuse and parental discord (Rubino et al., 2009); sexual and emotional abuse (Daalman et al., 2012) and sexual abuse and victim of serious injury, illness or assault (Bebbington et al., 2004). Additionally, a population study examining specificity between different adversities and psychotic outcomes found that emotional neglect as well as physical, sexual and emotional abuse were equally associated with hallucinations, delusions and paranoia (Martine van Nierop et al., 2014). Thus, even studies with greater methodological rigor, regarding specificity, show mixed results as to which specific adversity drives the risk for psychosis. Further to this, adversities often appear together in persons with psychotic disorders (DeRosse et al., 2014; Ramsay et al., 2011; Rosenberg et al., 2007).

While the body of psychosis research has been focused upon a search for specific adversities as risk factors, research into mechanisms and phenomenology of childhood and adolescent adversity may provide clues as to why this approach has not found conclusive results. The focal
point in this research has been that persistent adversities are considered traumatizing if they are overwhelming and prevent the organism’s return to physiological homeostasis. This mechanism is irrespective of the specific acts or lack of acts, and any abuse or neglect is potentially traumatizing (De Bellis, 2001). There are many examples of unspecific effects of traumatization: the immediate brain response of increased locus coeruleus activity is seen in relation to both fight, flight and freeze responses (De Bellis, 2001; Perry and Pollard, 1998); the stress of different adversities, which is suggested to exert similar effects on cortico-limbic development (Teicher, 2010); and findings of individuals exposed to abuse and/or neglect having changes in brain connectivity networks as a group when compared to persons with no such history (Teicher et al., 2014).

Additionally, no trauma treatment targets single adversities, but rather the consequences caused by traumatization. CBT, which is considered the most validated treatment for children and adolescents with PTSD (Silverman et al., 2008) focuses upon the cognitive, emotional and social consequences of traumatization (Cohen et al., 2006). Likewise, neurodevelopmental treatments seek to improve brain function where it has been impeded by traumatization (Perry, 2006).

An investigation of the construction of adversity assessment tools also calls into question the possibility that specific adversity subcategories tap discrete and encapsulated experiences. For example, in the construction of the Childhood Trauma Questionnaire (CTQ) the created subcategories were not discrete: physical abuse was associated with therapist observation of both physical and emotional abuse (Bernstein et al., 2003).

The mixed findings of associations between different specific adversities and risk of psychosis together with correlations between specific adversities, may suggest that the adversities represent an integrated phenomenon. This raises the issue of whether the focus upon the influence of specific adversities in psychosis research is preventing us from seeing their full effect.

Alongside the substantial overlap between different childhood and adolescence adversities, there are indications of a dose-response effect on the risk of psychosis (Anda et al., 2006; Arseneault et al., 2011; Fawzi et al., 2013; Heins et al., 2011; Lataster et al., 2006; Shevlin et al., 2007; Whitfield et al., 2005). However, some studies have not found an effect (Fisher et al., 2010; Sahin et al., 2013). A dose-response effect implies that each adversity adds extra risk or has an interactive effect in the development of psychosis.

The current study aims, in a case-control design, to explore the relation between adversity specificity and dose-response effect in an epidemiological sample of persons with non-affective first-episode psychosis compared to a non-clinical control group.
2. Method

2.1. Participants

2.1.1. FEP group
Denmark has a nationwide early intervention program (OPUS) for persons with first-episode psychosis (FEP) (Petersen et al., 2005). Inclusion criteria at the time of the study were an ICD-10 diagnosis F20-29, except F21, that was not due to organic causes; as well as being in the 18-35 age range. Exclusion criteria were a previous diagnosis of psychosis. Substance abuse was not an exclusion criterion. The catchment area was Region Zealand (N = 816,359). Everyone commencing treatment between April 1 2011 and April 1 2013 was approached for participation. Additional study criteria were exclusion of persons with insufficient Danish skills to complete the interviews.

2.1.2. Control group
Inclusion criteria were living in Region Zealand, Denmark and being 17 to 34 years of age. Exclusion criteria were any previous psychiatric disorder and insufficient Danish skills to complete the interview. Substance abuse was not an exclusion criterion. Control persons were matched 1: 1 by gender, age (+/- 1 year), and parental education (+/- 1 one on a 5 point scale). Control persons were recruited through advertisement in newspapers, educational institutions, libraries, and sport clubs, and by word of mouth. They were included from October 1 2013 to May 22 2014. The advertisement did not mention trauma.

2.2. Measures

2.2.1. Adversities
The Childhood Trauma Questionnaire (CTQ) was used for trauma assessment (Bernstein et al., 2003). We used the Danish validated version (Bernstein and L. Fink, 2011). The CTQ consists of five subcategories, each represented by five questions. The CTQ subcategories were dichotomized using the cut-off scores from moderate to severe as suggested by Bernstein et al. (Bernstein and L. Fink, 2011). These were six for males and females for sexual and physical abuse, eight for males and ten for females for emotional abuse, seven for males and females for physical neglect, and 13 for males and 12 for females for emotional neglect. Separation and institutionalization were assessed with the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005; Smith et al., 2002).
2.2.2. Psychopathology
The OPCRIT diagnostic system was used to obtain ICD-10 diagnoses, based on patient records and a Positive and Negative Symptom Scales (PANSS) interview (Kay et al., 1987). The latter was extended to include life-long symptoms (McGuffin et al., 1991). A psychologist or medical doctor trained by a senior psychiatrist administered the instruments. Control participants were screened with the Mini International Neuropsychiatric Interview (MINI) 6.0 for any prior and present psychiatric diagnoses (Sheehan et al., 2008, p. 0). The first author administered it. Psychiatric illness in first-degree relatives included depression, bipolar, autism and psychotic disorders. These were assessed by interview, either of the person in question or for the FEP group the parent.

2.2.3. Demographic data
Parents’ socio-economic status was chosen as the highest educational degree achieved by either parent, with whom the patient had lived. We chose parental educational level as a proxy measure for socio-economic status, because it has been found to be associated with both trauma and psychosis (Croudace et al., 2000; Sidebotham and Heron, 2006). It was measured on a 5-point scale.

2.2.4. Reliability
Seventeen interview videos and vignettes were randomly drawn from the FEP group for reliability testing of the psychiatric diagnoses. Four clinicians rated these independently. We found an overall agreement of 82 % and a median kappa of 0.52.

2.3. Statistical analysis
The IBM SPSS Statistics for Windows, Version 22.0 was used for all analyses. Frequency graphs of continuous measures were inspected visually to determine approximation of the normal distribution. Two-tailed Spearman’s Rank order correlations were used because of the binomial and not normal distribution of the data. Binary logistic regression analyses were performed with psychosis as the dependent variable and age, gender, parents’ socioeconomic status, first-degree psychiatric illness and adversities as covariates. Covariates were included using a priori reasoning rather than step-wise selection. Significant adversities were included in the final model to fit the best predictive model and investigate independent adversity influence. Multicollinearity was not an issue with the generally low correlations. The Hosmer-Lemeshow goodness-of-fit test was applied to all logistic regression analyses and the models fitted well. All CTQ subcategory interactions were examined and none was significant. Interactions between gender and sexual abuse were examined due to theoretical considerations and none was found (OR = 2.23, CI = 0.06-79.8, p = 0.661). CTQ
missing values were set at a conservative lowest score if there was only one out of five missing scores from a category. This occurred twice. We explored dose-response effects by scaling the number of adversities, including CTQ subcategories, separation and institutionalization.

2.4. Ethics

All participants received oral and written study information. For persons with FEP, it was clearly stated that they could withdraw their consent at any time, and that participation had no impact on their treatment. Control persons received DKK 400 equal to EURO 54 as compensation for their time and contribution. The protocol was submitted to the Regional Ethics Committee and pre-approval was found unnecessary as it only implicated questionnaires and interviews. The Data Protection Council, Region Zealand, approved data management (journal no. 12-000660).

3. Results

3.1. Sample description

We obtained full data on 101 persons with FEP and 101 matched control persons. Of the 194 eligible persons with FEP, 93 (48 %) were not included. Three due to insufficient Danish skills; 51 did not wish to participate; 14 withdrew their consent after the first interview; 18 were impossible to contact; and 11 were interviewed before the CTQ was included in the protocol. There were more females (44 %, $\chi^2 = 7.5$, $p < 0.01$) and fewer persons diagnosed with schizophrenia in the excluded group (67 %, $\chi^2 = 26.9$, $p < 0.001$). The median age was not statistically different for the excluded persons (Mann-Whitney U 4120, $p = 0.053$).

Sixteen control candidates were excluded. Nine due to depression, four due to hypomanic or manic episodes, two due to anxiety disorders and one due to already diagnosed and medically treated ADHD. The characteristics of the participants are presented in Table 1.

3.2. Adversity characteristics

Eighty-nine percent of the FEP group had at least one adversity compared to 37 % in the control group; and 52 % reported three or more adversities compared to 7 % in the control group. More than a third of the persons with FEP were separated from one or both parents due to other reasons than divorce, compared to seven percent in the control group. Institutionalization or foster care was reported more often in the FEP group with almost one fourth compared to two percent.
The variation of duration of institutionalization in the FEP group was large and the median was 2.8 years (range 0.01-12). The median duration of separation was four years (range 0.2 - 18 years). In the FEP group the reported causes of separation were that the parent was violent (13 %); left them (13 %); was sick or ill (13 %); or unable to take care of them (10 %). For 46 % there were other reasons, and 5 % (n = 2) did not know why they had been separated.

3.3. Amount of adversity

Figure 1 presents the number of reported adversities, including CTQ subcategories, separation and institutionalization. The pattern was different in the two groups. There was a decline in the number of adversities in the control group, with the majority having experienced none or one adversity. In the FEP group, the majority reported several adversities, with more than half reporting three or more.

Table 2 presents the odds ratios for psychosis with increasing number of adversities. For every extra adversity the risk of psychosis increased two and half times. The ORs increased for each extra adversity, and were not significantly higher for one and two adversities but for three and more adversities.

3.4. Adversity relations

Tables 3 and 4 present correlations and regression analyses for specific adversities. The regression analyses were conducted in three steps with psychosis as outcome. In the first model, gender, age, first-degree psychiatric disorder and parent’s socio-economic status were adjusted for; in the second, additionally other CTQ subcategories; and in the third, additionally separation and institutionalization. All CTQ subcategories were significantly higher in the FEP group, with increased risks of about four to 17 times. All CTQ subcategories were significantly correlated with at least two other subcategories with the highest being emotional abuse and emotional neglect (p=.502), and emotional and physical neglect (p=.458). When they were adjusted for other CTQ subcategories, each of them dropped to half the size. Physical abuse alone lost its significance entirely when all CTQ subcategories, institutionalization and separation were adjusted for.

Institutionalization was correlated only with physical abuse and separation. Its OR dropped from 18 to 13 and remained significantly higher when all adversities were adjusted for. The OR for separation dropped from a significantly higher seven to non-significantly higher three when adjusted for other adversities. Death of a parent was reported by less than a tenth in both groups and was thus not significantly different. We examined age at the parent’s death, but equally found no
significant difference: median 12 years old in the FEP group and 14 years old in the control group (Mann-Whitney U=14.5, p=0.347).

4. Discussion

This study explored specificity and dose-response effects of reported adversities in 101 persons with non-affective FEP and 101 matched control persons. We found a dose-response effect, with an increasing number of adversities increasing the risk of psychosis. Specific adversities’ contribution to the overall risk of psychosis decreased when other adversities were adjusted for.

The much greater amount of adversity in the psychosis group is consistent with previous research (Filippo Varese et al., 2012). We wish to highlight the high number of institutionalizations in the FEP group as it is a compelling sign of hardship that is unlikely to be misremembered and which only takes place in circumstances where a parent is unable to care for a child (Andersen, 2008). Two studies found a similar prevalence of institutionalization in psychosis groups (35 and 41 %) (Robins, 1996; Rosenberg et al., 2007) while a third did not (4.4 %) (Fisher et al., 2010).

All the ORs decreased when other adversities were adjusted for. We suggest this reflects a shared effect of the adversities on risk of psychosis. A shared effect that for most adversities was larger than their individual effect. We could have concluded that physical abuse was unrelated to the overall risk of psychosis. Instead, we want to draw attention to the fact that all, but one, of those who reported physical abuse, reported other CTQ subcategories. The effects of physical and sexual abuse were lost due to the statistical analysis that juxtaposed the adversities instead of combining them. Thus, it seems the adversity categorization prevented us from seeing the effect of the adversity load as a whole. It may be that every group of persons with psychosis will have a different adversity profile but a similar overall prevalence. This would explain why different studies find different adversities to increase the risk for psychosis (Daalman et al., 2012; Fisher et al., 2010; Rubino et al., 2009; Shevlin et al., 2007). For example, two studies found reports of emotional abuse in 11 and 70 % of their FEP groups using the same assessment instrument (Spidel et al., 2010; Wang et al., 2013). Thus, we suggest that the type of adversity, which represents specific traumatic instances, is less important than the fact that the individual has been exposed.

While the type of adversity appears less important for the development of psychosis, the number of
adversities seems crucial. This dose-response effect has been found in several studies (Anda et al., 2006; Arseneault et al., 2011; Fawzi et al., 2013; Heins et al., 2011; Lataster et al., 2006; Shevlin et al., 2007; Whitfield et al., 2005), but not in the one which is most similar to ours (Fisher et al., 2010). This is probably due to the control group exclusion criteria that excluded persons with psychotic symptoms but not other psychiatric disorders (Fisher et al., 2010). This would decrease the ORs because adversities are associated with other psychiatric disorders (Kessler et al., 2010). In general, these findings imply that the amount of adversity is essential for understanding the increased risk of psychosis.

The childhood trauma literature, suggests that adversities are damaging if they are overwhelming and persistent. It is likely that the adversities examined in this study were overwhelming as we applied criteria to capture severe adversities: moderate to severe CTQ cut-off scores were used; separation from parents was due to other reasons than divorce; and the reality that institutionalization is only considered when parents are unable to care for their child (Andersen, 2008). Parental death was not significantly different in the FEP group compared to the control group. This finding is similar to others (Filippo Varese et al., 2012) and perhaps suggests that parental death is not an adversity that overwhelms the individual in many circumstances.

Persistence was also apparent as 77% of those in the psychosis groups with CTQ adversities reported that at least one negative CTQ event occurred often or very often or that at least one positive incidence (such as feeling loved) occurred rarely or never. Thirty percent of the remaining 23% of the FEP and adversity group reported more than one CTQ adversity. Additionally, institutionalization represents persistent hardship; both in terms of the time spent in an institution and in terms of time that is required to ascertain that placement is the best option (Andersen, 2008). Furthermore, four of the remaining 23% of the FEP and adversity group reported to have been institutionalized. Therefore, we advocate that the severity and the persistence of traumatization were considerable in the FEP group, and hence that severity and persistence were characteristic for the adversities associated with an increased risk of psychosis.

Severity and persistence have been conceptualized to be what separates traumatization from the unavoidable accidents that everyone experiences during upbringing (Grayson J., 2006; Perry, 2002; Teicher et al., 2003). This conceptualization is implicit in the CTQ as it measures both the severity and the regularity of adversities. However, we suggest that a nomenclature, which explicitly highlights severity and persistence, would benefit the psychosis research.
The importance of severity and persistence of childhood and adolescent traumatization is supported by the findings of morphological and functional brain alterations found in exposed populations (Choi et al., 2012; Chugani et al., 2001; Kelly et al., 2013; Teicher et al., 2014, 2012; Thomas and De Bellis, 2004). Removal from traumatizing environments improves the later outcomes of emotional, cognitive and psychiatric difficulties (Perry, 2002; Teicher et al., 2003).

Several mechanisms have been suggested to confer adversities’ risk on psychosis. One of the most explored is the general stress-response (Howes and Murray, 2014; Myin-Germeys and van Os, 2007; Read et al., 2014): the Limbic-Hypothalamic-Pituitary-Adrenal (LHPA) –axis, which has been found altered in persons exposed to abuse and/or neglect (Bernard et al., 2010; Bruce et al., 2009; Hunter et al., 2011; Perry and Szalavitz, 2007) and in persons with psychosis (Borges et al., 2013; Ciufolini et al., 2014; Garner et al., 2009; Walker et al., 2008). As a general response to overwhelming situations, this system fits well with the importance of severity and persistence. Some evidence suggest that psychosis is an outcome of changes in the hippocampus (Maras and Baram, 2012) and dopamine responses due to over-activation of the LHPA-axis (Barker et al., 2015; Howes and Murray, 2014). It is established that more stress causes more detrimental changes in hippocampus (Maras and Baram, 2012) and it has also been found that higher levels of stress are associated with more positive symptoms of psychosis in people at ultra high risk (Pruessner et al., 2011). However, future research that includes persistence and severity of adversities in relation to these systems in people with psychosis could further our understanding of their importance.

Another mechanism involves dysfunctional emotional processing (Birchwood, 2003). Disturbing emotional experiences that are insufficiently regulated can result in dysfunctional emotional processing. The disturbing emotional experiences are represented by the CTQ and it is likely that children were unable to regulate their responses to these experiences as many of the adversities happened within the family. Ninety-one percent of the FEP and adversity group reported abuse or neglect within the family (emotional abuse, emotional and physical neglect) compared to 27 % in the control group. More, persistent, severe traumatization signifies more disturbing emotional experiences and a greater risk of traumatization within the family. In support, dysfunctional emotional processing has been found to be a mediator between childhood adversities and psychotic symptoms (Kramer et al., 2012).

Our data suggest the risk of psychosis is not dependent on specific adversities. It is possible that factors such as severity, persistence and the relationship to the abuser are more important in relation
to psychosis. However, on the individual level, the actual experiences are important. They are what form our inner life and our sense of self (Beck, 1976; Bowlby, 1983). The latter can be expressed in the psychotic symptoms as adverse experiences influencing the contents of hallucinations (Hardy et al., 2005). However, we suggest a holistic view of traumatization, with special attention being paid to shared effects of adversities in the search for causal mechanisms and in treatment.

4.1 Strengths and limitations

The nature of a cross-sectional study rules out strong claims of cause-effect relations. The idea of shared effects and the suggested mechanisms are hypotheses and other interpretations of our data are possible. The current study contained recall bias, an issue that has been addressed in several studies. Memories of adversities seem reasonably stable in persons with FEP (Fisher et al., 2011), and similarly biased for persons with and without psychopathology (Fergusson et al., 2000). Regarding first-degree relatives’ psychiatric disorders, relatives of the FEP group might have confirmed or added information during their parallel assessment. The confidence intervals of dose-response ORs were very wide, and grew wider with increasing number of adversities. This reflects an uncertainty in our results, due to the lower and lower frequencies in the control group.

Due to the organization of the Danish Health Service, we expect that almost every incidence of psychosis has been referred to the study. We regard the FEP group representative of the catchment area even though 48 % of the eligible persons with FEP were not included. They differed with respect to diagnosis, which may be due to different diagnostic assessments and not actual differences since the clinical diagnoses only occasionally were assessed using the OPCRIT. Furthermore, the clinical diagnoses were obtained at the beginning of treatment while our assessment began an average three months later. We do not expect this difference to have affected our results as most of the excluded were instead diagnosed with paranoid psychosis (11 %), unspecified psychosis (10 %) and acute psychosis (9 %). The first two are expected to have similar rates of adversities and based on theoretical considerations, acute psychosis should be associated with higher rates than schizophrenia (Myin-Germeys and van Os, 2007). The presence of more men in the included compared to the excluded group could have given a lower prevalence of adversities, as women with psychosis have been found to have more adversities in other studies (Fisher et al., 2009). The matching of parental socioeconomic status has decreased the risk that our findings are confounded. It strengthens the possibility that childhood and adolescent adversities are the actual risk factors for psychosis. Reliability was good and sample size satisfactory to perform the sought
analyses.

4.2 Future research and clinical implications

It is evident from our study that a person with FEP who discloses one adversity is likely to have experienced others as well. Assessment should therefore be thorough and strive to include all adversities. The current FEP group mentioned numerous adversities additional to those in the assessment tools. These included early hospitalizations and physical illness; ongoing bullying; witnessing death in the family; violence and substance abuse in the family; and physical illness of a parent.

Studies of specific types of adversities should assess all possible adversities to prevent confounding. Furthermore, studies exploring both specific and shared effects should include factors that appear to influence traumatization such as severity, persistence and the involvement of caregivers.

Our results suggest that FEP interventions should include traumatization in their treatment approach. For example, psycho-educational material could be improved by inclusion of information on how adverse experiences can affect people. Some treatments have had success with addressing trauma, such as CBT for PTSD in persons with psychosis (Schäfer and Fisher, 2011). In addition, new studies are under way, such as the pilot clinical trial TRauma-Informed Psychotherapy for Psychosis (TRIPP) (Bendall, Sarah, 2014). TRIPP focus upon the symptoms of trauma along with the creation of safety and shared formulation.

Besides improving treatment, preventive political and social initiatives could decrease the degree and consequences of abuse and neglect that children and adolescents are exposed to. Such initiatives could include education for children about self protection and help-seeking; education in early detection of child abuse for society in general and for the nursing, medical and psychologist students; and improvement of the societal views that include intergenerational inheritance and don’t blame but assist perpetrators (Longden, 2012).

Role of funding source

The study was supported by The Regional Health and Research Foundation, Zealand (AMT Grant number 12-000095); and The Lundbeck Foundation (AMT Grant number R93-A8804).
Contributors

A.M. Trauelsen, U.H. Haahr, J.E. Jansen, M.B. Pedersen, HG.L. Nielsen and E. Simonsen designed the study and wrote the protocol. A.M. Trauelsen managed the literature searches and statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

Acknowledgements

We are grateful to the interviewees and the clinicians who put their time and effort into the project.

We thank Antonia Bifulco for permission to use the CECA-Q questions.

References


Figure 1. Number of reported adversities including sexual, physical, emotional abuse, physical and emotional neglect, separation and institutionalization in persons with FEP (n=101) and matched control persons (n=101).
### Table 1. Demographic data for persons with the first-episode psychosis (n=101) and matched control persons (n=101)

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>FEP, n (%)</th>
<th>Controls, n (%)</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (74)</td>
<td>75 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (53)</td>
<td>26 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, median (range)</strong> a</td>
<td>22.5 (18 - 34)</td>
<td>22 (18 - 33)</td>
<td>Z=0.087&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.931</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>92 (91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia simplex</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective psychosis</td>
<td>4 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>5 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Danish</td>
<td>82 (86)</td>
<td>85 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, other</td>
<td>11 (12)</td>
<td>13 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black African</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not finished public school</td>
<td>5 (5)</td>
<td>0</td>
<td>64.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Public school (9-10 years)</td>
<td>68 (68)</td>
<td>19 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gymnasium (12-13 years)</td>
<td>13 (13)</td>
<td>57 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University/completed vocational education</td>
<td>14 (14)</td>
<td>25 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parent’s socio-economic status c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td>3.19</td>
<td>0.527</td>
</tr>
<tr>
<td>Lower skilled</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher skilled</td>
<td>38 (38)</td>
<td>40 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer theoretical</td>
<td>28 (28)</td>
<td>28 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>7 (7)</td>
<td>13 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First Degree Psychiatric Disorder d</strong></td>
<td>25 (30)</td>
<td>15 (16)</td>
<td>4.85</td>
<td>0.028</td>
</tr>
</tbody>
</table>

<sup>a</sup> Age at the Childhood Trauma Questionnaire interview.
<sup>b</sup> Mann-Whitney 5065.
<sup>c</sup> The highest parental vocational education.
<sup>d</sup> Reported psychosis, bipolar, autism and depression in first degree relatives.
Table 2. Logistic regression analysis for number of adversities in persons with FEP (n=101) and matched control persons (n=101).

<table>
<thead>
<tr>
<th>Adversities</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>One adversity</td>
<td>19 (19)</td>
<td>21 (21)</td>
<td>0.95</td>
<td>0.45-1.98</td>
<td>0.88</td>
<td>7.41</td>
</tr>
<tr>
<td>Two adversities</td>
<td>18 (18)</td>
<td>9 (9)</td>
<td>1.84</td>
<td>0.82-4.87</td>
<td>0.13</td>
<td>2.29</td>
</tr>
<tr>
<td>Three adversities</td>
<td>18 (18)</td>
<td>4 (4)</td>
<td>5.06</td>
<td>1.59-16.17</td>
<td>0.01*</td>
<td>7.49</td>
</tr>
<tr>
<td>Four adversities</td>
<td>11 (11)</td>
<td>1 (1)</td>
<td>12.78</td>
<td>1.56-105</td>
<td>0.02*</td>
<td>5.62</td>
</tr>
<tr>
<td>Five or more adversities</td>
<td>24 (24)</td>
<td>2 (2)</td>
<td>12.95</td>
<td>2.84-59.00</td>
<td>0.001**</td>
<td>10.96</td>
</tr>
<tr>
<td>Linear trend&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>2.55</td>
<td>1.91-3.40</td>
<td>&lt;0.001**</td>
<td>39.97</td>
</tr>
</tbody>
</table>

<sup>a</sup>Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent’s socio-economic status

<sup>b</sup>Adversities included are CTQ subcategories, separation and institutionalization before age 18

<sup>c</sup>Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent’s socio-economic status

<sup>d</sup>Institutionalization or foster care.
Table 3. Spearman rank correlation analysis of CTQ subcategories, separation and institutionalization in persons with FEP (n=101)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physical Abuse</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Sexual Abuse</td>
<td></td>
<td>.348&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Emotional Abuse</td>
<td>.237&quot;</td>
<td></td>
<td>.280&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Emotional Neglect</td>
<td>.327&quot;</td>
<td></td>
<td>.260&quot;</td>
<td>.502&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Physical Neglect</td>
<td>.225&quot;</td>
<td>.188</td>
<td>.234&quot;</td>
<td>.458&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Institutionalization</td>
<td>.338&quot;</td>
<td>.130</td>
<td>.167</td>
<td>.039</td>
<td>.122</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Separation*</td>
<td>.250&quot;</td>
<td>.057</td>
<td>.204&quot;</td>
<td>.101</td>
<td>.114</td>
<td>.627&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Death of parent*</td>
<td>.046</td>
<td>-.061</td>
<td>.051</td>
<td>.071</td>
<td>.074</td>
<td>.150</td>
<td>.358&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Any Adversity</td>
<td>.318&quot;</td>
<td>.233&quot;</td>
<td>.549&quot;</td>
<td>.367&quot;</td>
<td>.495&quot;</td>
<td>.091</td>
<td>.124</td>
<td>.005</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*aInstitutionalization or foster care, separation or death of parent before age 18.

*P<0.05

**P<0.01
Table 4. Logistic regression analyses for childhood and adolescence adversities with the CTQ in persons with FEP (n=101) and matched control persons (n=101)

<table>
<thead>
<tr>
<th>Type of trauma</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR^a</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR^b</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR^c</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Abuse</td>
<td>24 (24)</td>
<td>4 (4)</td>
<td>8.51</td>
<td>2.30-31.50</td>
<td>&lt;0.01**</td>
<td>10.3</td>
<td>4.13</td>
<td>0.87-19.54</td>
<td>0.073</td>
<td>3.2</td>
<td>5.76</td>
<td>0.99-33.55</td>
<td>0.051</td>
<td>3.8</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>37 (37)</td>
<td>14 (14)</td>
<td>3.53</td>
<td>1.59-7.83</td>
<td>&lt;0.01**</td>
<td>9.6</td>
<td>0.97</td>
<td>0.34-2.78</td>
<td>0.958</td>
<td>&lt;0.01</td>
<td>0.72</td>
<td>0.23-2.28</td>
<td>0.580</td>
<td>0.3</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>64 (63)</td>
<td>17 (17)</td>
<td>7.33</td>
<td>3.54-15.21</td>
<td>&lt;0.001**</td>
<td>28.7</td>
<td>3.27</td>
<td>1.41-7.55</td>
<td>&lt;0.01**</td>
<td>9.91</td>
<td>3.71</td>
<td>1.50-9.20</td>
<td>&lt;0.01**</td>
<td>8.0</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>44 (44)</td>
<td>5 (5)</td>
<td>16.93</td>
<td>5.41-52.98</td>
<td>&lt;0.001**</td>
<td>23.6</td>
<td>3.59</td>
<td>1.20-16.87</td>
<td>&lt;0.05*</td>
<td>5.0</td>
<td>4.44</td>
<td>1.13-17.55</td>
<td>&lt;0.05*</td>
<td>4.5</td>
</tr>
<tr>
<td>Physical Neglect</td>
<td>59 (58)</td>
<td>17 (17)</td>
<td>6.23</td>
<td>2.99-13.00</td>
<td>&lt;0.001**</td>
<td>23.8</td>
<td>2.98</td>
<td>1.27-6.97</td>
<td>&lt;0.05*</td>
<td>6.3</td>
<td>3.45</td>
<td>1.38-6.65</td>
<td>&lt;0.01**</td>
<td>7.0</td>
</tr>
<tr>
<td>Separation</td>
<td>39/95 (41)</td>
<td>7 (7)</td>
<td>7.45</td>
<td>2.78-19.94</td>
<td>&lt;0.001**</td>
<td>16.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Death of parent &lt; age 18</td>
<td>7/94 (7)</td>
<td>6 (6)</td>
<td>1.20</td>
<td>0.32-4.53</td>
<td>0.788</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Institutionalization &lt; age 18</td>
<td>23/97 (24)</td>
<td>2 (2)</td>
<td>17.55</td>
<td>2.20-140</td>
<td>&lt;0.01**</td>
<td>7.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.1</td>
<td>1.08-159</td>
<td>&lt;0.05*</td>
<td>4.1</td>
</tr>
<tr>
<td>Any adversity</td>
<td>90 (89)</td>
<td>37 (37)</td>
<td>18.12</td>
<td>7.39-44.43</td>
<td>&lt;0.001**</td>
<td>40.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OR, Odd ratio; CI, confidence interval
^a Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status
^b Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status and other CTQ categories.
^c Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status, other CTQ categories and separation and institutionalization.
^d Institutionalization or foster care.
*p<0.05, **p<0.01
Letter

Severity and persistence versus type of childhood adversity in non-affective first-episode psychosis

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d Centre for Youth Mental Health, the University of Melbourne, Australia
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f Department of Psychology, University of Copenhagen, Copenhagen, Denmark
g Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

We thank Dr. Vishal Bhavsar for the opportunity to clarify our reasoning and viewpoints. We agree with many of his thoughtful comments and believe that several potential disagreements can be settled by our clarification.

A first point of clarification concerns conceptualization. Dr. Bhavsar seems to be under the impression that we are implying that certain adversities are unimportant for the development of psychosis because we demonstrate that large parts of the statistical associations between individual adversities (such as physical and sexual abuse) and psychosis are lost when we adjust for other adversities. We are in fact concluding the opposite. We suggest that odds ratios are reduced precisely because individual adversities co-occur. We suggest that these experiences are often inextricably linked, that they share factors, circumstances and effects of traumatization that increase the risk of psychosis. We suggest that the overall severity and the persistence of these shared common aspects of traumatization are more important than the type of adversity itself. This is

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** Financial support. The study was supported by The Regional Health and Research Foundation, Zealand (AMT Grant number 12-000095); and The Lundbeck Foundation (AMT Grant number R93-A8804).
certainly different from an approach looking for the independent effects of individual adversities. We agree that one approach does not rule out the other, but we wish to introduce this new way of conceptualising adversity in the psychosis field.

We understand that our conceptualization differs from the more traditional way of interpreting logistic regression analysis. Usually, one is interested in each individual variable’s unique prediction of the outcome (here, psychosis). We have paid more attention to the pattern of the reductions in these predictions (odds ratios) and to the pattern of inter-correlation across all the adversities. Our reasons for using this conceptualization are that it might explain previous conflicting results. First, studies of similar populations find different prevalences for the same types of traumas, i.e. two studies found that respectively 11 and 70% had been exposed to emotional abuse, using the CTQ (Spidel et al., 2010; Wang et al., 2013). Second, when adjustments for other adversities are performed, different adversities are found to be the unique predictors of psychosis (Bebbington et al., 2004; Fisher et al., 2010; Shevlin et al., 2007). We sought to arrive at a conceptualization that could make sense of these important conflicting findings along with our own.

We also sought to encourage researchers to recognize our considerations when they are interpreting their results. We believe that in studies of single adversities, there should be an awareness of possible confounding as results may not be specific for that one type of adversity.

We will now try to elucidate specific issues that Dr. Bhavsar has brought forth.

First, we did not suggest that “overlapping confidence intervals ... indicates that the underlying effect is of a similar magnitude across adversities”. We stated, “The confidence intervals of dose-response ORs were very wide, and grew wider with increasing number of adversities. This reflects an uncertainty in our results, due to the lower and lower frequencies in the control group.”

Secondly, the review of physical abuse that Dr. Bhavsar mentions seems to support our viewpoint. It states that “The relationship between physical abuse and long-term characteristics may also be affected by occurrence of other forms of maltreatment (e.g., sex abuse)” and that “Other maltreatment variables—such as age at onset and at termination of abuse and duration, frequency, and severity of abuse—have not been sufficiently measured and explored in the physical-abuse literature” (Malinosky-Rummell and Hansen, 1993).
With regards to adversity specificity and clinical implications, interventions for childhood adversity in people with psychosis are in their infancy, but those that are available have not developed treatments for specific adverse experiences (such as sexual abuse for example) but rather have focussed on targeting the effects of traumatisation (post-traumatic stress disorder, dissociation, hallucinations) regardless of the experience (Bendall, S, 2014; van den Berg et al., 2015). In fact, interventions to treat specific adversities make little sense considering that very few people with psychosis have experienced only one adversity type. We believe this adds support to our argument. This is not to say that the individual experience is not extremely important to explore in psychotherapeutical treatment, but that the structure and process of treatment is similar regardless of the type of adversity experienced.

We have carefully reconsidered our interpretations in light of Dr. Bhavsar’s letter and believe they are statistically and conceptually sound. It seems that we mainly agree with Dr. Bhavsar, which we hope we have succeeded in clarifying. We also hope the field will consider our ideas as they appear crucial if we “are going to intervene, or better understand adversity effects” as Dr. Bhavsar rightly recommends.

We thank Professor Henry Jackson for helpful statistical and conceptual discussions.

and Reprocessing vs Waiting List for Posttraumatic Stress Disorder in Patients With a Psychotic Disorder: A Randomized Clinical Trial. JAMA Psychiatry 72, 259–267.

Paper 2

Childhood adversities: social support, premorbid functioning and social outcome in first-episode psychosis and a matched case-control group

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³ Financial support. The study was supported by The Regional Health and Research Foundation, Zealand (AMT Grant number 12-000095); and The Lundbeck Foundation (AMT Grant number R93-A8804).

³ This paper is part of the OPUS Zealand research project: Family Intervention in First-episode Psychosis. An investigation of metacognition, expressed emotion and caregiver experiences. From January 1. 2012 the project has the following research group: Erik Simonsen, MD, PhD (PI). Ulrik Haahr, MD (PI). Christopher Hoeier Trier, MSc in Psychology. Marlene Buch Pedersen, MSc in Psychology. Hanne-Grethe Lyse Nielsen, RN. Mette Sjøestroem Petersen, MA (ed) in Educational Psychology. Jens Einar Hansen, PhD. Ulf Soegaard, MD. Anne Marie Trauelsen, MD. From September 1. 2014 Signe Dunker Svendsen, RN. From Psychiatric Research Unit, Psychiatry Region Zealand, Denmark. Early Psychosis Intervention Center, Psychiatry East Region Zealand, Denmark.
Abstract

Objective: The establishment of childhood adversities as risk factors for non-affective psychosis have derived a need to consider alternative interpretations of several psychosis related factors. This paper sought to examine premorbid adjustment trajectories and social outcome factors in relation to childhood adversities. Perceived support has been found to decrease the risk of post-traumatic stress disorder, and we wished to compare perceived support in people with first-episode psychosis to non-clinical control persons and explore its relation to childhood adversities.

Method: Every individual presenting with a non-affective first-episode psychosis (F20 - 29, except F21) in Region Zealand over a two year period was approached for participation and the 101 consenting participants were matched to 101 people with no psychiatric disorders. Comprehensive demographic data were collected. Assessment instruments included the Premorbid Assessment Scale, the Global Assessment of Functioning scale and the Childhood Trauma Questionnaire. The latter represented the childhood adversities in addition to parental separation and institutionalization.

Results: There were no associations between number of childhood adversities and different social or academic premorbid trajectories. Those with more adversities had lower global functioning the year prior to treatment start and reported lower rates of perceived support during childhood along with less current face-to-face contact with family members. Lack of peer support remained a significant predictor of psychosis when adversities were adjusted for and it diminished the risk of psychosis caused by childhood adversities by 10%.

Conclusion: Childhood adversities may not predict specific premorbid trajectories, but have an effect on global functioning when the psychosis has begun. Perceived support, especially from peers, may be important in the development of psychosis, and those with more adversities may represent a vulnerable subgroup who need more assistance to increase and maintain supportive networks.

Keywords
Premorbid adjustment; global functioning; perceived support; social network; schizophrenia
Introduction

Childhood adversities are now established risk factors for non-affective psychosis (Varese et al., 2012). They may well add knowledge to our interpretation of other recognised socio-environmental risk and outcome factors and to our developmental models of psychosis. These factors include premorbid adjustment, years of education, global functioning and occupational and living status. Deterioration of premorbid social and academic adjustment has most often been presented as evidence of an underlying neurodegenerative encephalopathy (Allen et al., 2013; Larsen et al., 2004), but recent findings suggest that it may additionally be affected by childhood adversities. One first-episode psychosis (FEP) study found that premorbid social adjustment was associated with childhood sexual and/or physical abuse (Conus et al., 2010) and a study of people with long-lasting psychosis found relations between childhood adversity and premorbid school and peer difficulties (Schenkel et al., 2005). Another FEP study found that childhood adversity was associated with poorer premorbid social and academic adjustment, though not with change in adjustment from childhood to adolescence (Stain et al., 2014).

Childhood adversities have also been found to be associated with decreased educational achievement (Boden et al., 2007) and lower employment rates (Widom, 2000) in the general population. In the psychosis literature the investigation of childhood adversities’ relation to other social factors has only just begun and the findings are mixed. One study of people diagnosed with schizophrenia found that childhood adversities were associated with current overall- but not social functioning (Gil et al., 2009), while a 66 % non-affective psychosis FEP study found no associations between childhood adversity and social activity (Duhig et al., 2015) and an Ultra High-Risk study of several childhood adversities found that only bullying predicted worse current functioning (Addington et al., 2013). Another study of people diagnosed with schizophrenia found that only some parts of social functioning (role functioning and intimacy) was poorer for those with a history of childhood sexual abuse compared to those without (Lysaker et al., 2001). An Ultra High-Risk follow-up study (at 2-14 years) found that for both transitioned and non-transitioned individuals, the total Childhood Trauma Questionnaire score predicted poorer social and vocational functioning, while no other predictor did, including DUP and baseline symptoms (Yung et al., 2015).

Also with regards to occupational status, Conus and colleagues found in a large study of 658 patients with FEP that those with sexual and/or physical abuse had lower rates of employment/occupation (Conus et al., 2010), while two smaller FEP studies found no association
between childhood adversity and current employment (Campbell et al., 2013; Duhig et al., 2015). A third small schizophrenia study found that those with childhood adversity were more likely to be employed (Spence et al., 2006). However, Spence et al. excluded people with PTSD who have been found to experience the highest rates of childhood adversity and to represent up to 39% (95% CI 23–55%) of a FEP sample (Bendall et al., 2012). Thus, the study has low representativeness.

Equally unclear are the findings concerning educational achievement where two FEP studies have found weak or no associations between childhood adversity and years of education (Ramsay et al., 2011) and (Ucok A. and Bikmaz S., 2007). These findings reflect the need for clarification of childhood adversities’ relation to both educational attainment and global and occupational status in people with non-affective psychosis, to increase our understanding of these outcomes.

In addition, factors of resilience have the potential to explain why some and not others develop psychiatric disorders. A meta-analysis of risk factors for PTSD found that having social support in the period after the triggering trauma decreased the risk of developing PTSD (Brewin et al., 2000). Furthermore, a prospective birth-cohort study found that having received paternal support and affection in childhood protected against the development of various psychiatric disorders at age 16-18 years (Lynskey and Fergusson, 1997), though no effect was found for maternal support and affection. In the psychosis literature, social support has mainly been represented by the size of current networks, which have been found to be smaller for people with psychosis than for non-clinical populations (Gayer-Anderson and Morgan, 2013). Some evidence suggests that the smaller networks represents a lack of close relations and not a lack of acquaintances (Macdonald et al., 2000). Having close relations is very similar to having perceived support as the latter also refers to the presence of confidants. Thus, it seems that there is indirect evidence that people with non-affective psychosis have lower levels of current perceived support. The importance of this proposition was recently established by a study of people with delusions, which showed that good current relationships increased people’s cognitive flexibility, leading to a decreased level of delusional experiences (Jolley et al., 2014). Correspondingly, a large population study of people from the age of 16 found associations between current lack of objective and perceived support and delusion-like experiences (Saha et al., 2012). This data suggest that there may be a lowered rate of perceived support during childhood and adolescence in people with non-affective FEP. In addition, the family is one of the primary sources of current support for people with psychosis (Jolley et al., 2014) and it seems that a large part of the childhood adversities that people with FEP report happen in the home-environment (Trauelsen et al., 2015). As any negative impact of childhood adversity
could reveal a plausible mechanism for decreased perceived support and a possible intervention
object, we wished to examine how current family contact related to childhood adversities.
This paper aimed to examine associations between childhood adversities and premorbid adjustment
trajectories and social outcome in a larger FEP sample. Furthermore, it sought to explore whether
perceived support in childhood and adolescence affected the risk of psychosis and how it related to
childhood adversities and whether childhood adversities affected current family contact in the FEP
group.

**Hypotheses**

i. Childhood adversities will be associated with poorer premorbid adjustment trajectories and poorer
global functioning in the year prior to treatment in the FEP group.

ii. Childhood adversities will be associated with poorer occupational and living status and fewer
years of education in both the FEP and a non-clinical control group.

iii. Perceived support is associated with a lower risk of FEP and is associated with childhood
adversities.

iv. Childhood adversities are related to current family contact in patients with FEP.

**Method**

**Participants**

**FEP group.** The sample has previously been described by our research group (Trauelsen et al.,
2015, n.d.). Denmark has a nationwide early intervention program (OPUS) for people with FEP.
Inclusion criteria for OPUS during the study were an ICD-10 diagnosis F20-29, except F21, and an
age of 18-35 years. Exclusion criteria were a previous diagnosis of non-affective psychosis. The
catchment area was Region Zealand (population = 816,359) and everyone who was included in
OPUS between April 1st 2011 and April 1st 2013 was approached for participation. Additional
criteria for the study were sufficient Danish skills to complete the interviews.

**Control group.** Inclusion criteria were living in the catchment area and being 17 to 36 years of age.
Exclusion criteria were previous or current psychiatric disorders and insufficient Danish skills to
complete an interview. Control persons were matched 1:1 by gender, age (+/-1 year), and parental
vocational education (+/-1 one on a 5-point scale). Control persons were recruited through
advertisements in newspapers, at educational institutions, libraries, and sport clubs and by word of
mouth. They were included from October 1st 2013 to May 22nd 2014.

**Measures**

*Childhood adversity and perceived support.* The Danish validated version of Childhood Trauma Questionnaire (CTQ) was used for trauma assessment (Bernstein et al., 2003; Bernstein and L. Fink, 2011). The CTQ consists of five subcategories, each represented by five questions. The CTQ subcategories were dichotomized to include adversities that were at least severe, as suggested by Bernstein et al. (Bernstein and L. Fink, 2011). Separation and institutionalization were assessed with the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005; Smith et al., 2002). Separation that was primarily due to divorce was not included. Number of adversities ranged from zero to seven and was calculated by combining the five CTQ subcategories with separation and institutionalization. Perceived support during childhood and adolescence was also assessed with questions from the CECA.Q. They read “Did you have any adults you could talk to about your problems or feelings, as a child and teenager?” and “Did you have any peers you could talk to about your problems or feelings, as a child and teenager?”

*Sociodemographic data.* Highest parental vocational education was chosen as a matching parameter due to its association with both childhood adversities and psychosis (Croudace et al., 2000; Sidebotham and Heron, 2006). It was measured on a 5-point scale. First-degree psychiatric illness included any psychosis, depression, bipolar and autism disorder and was assessed by interview. Years of education referred to elementary school and high school and not vocational or university education. Family contact, living and occupational status were based on the Lehman Quality of Life Interview, translated by the TIPS research group (Lehman, 1988; Melle et al., 2010). Family contact concerned the year prior to treatment and was assessed with a 5-point scale ranging from 1 (everyday) to 5 (never). Living status concerned status at treatment start and was assessed with a 4-point scale: 1. Independent 2. Independent w. support, 3. Institution and 4. Without housing. Occupational status consisted of six categories which were redefined as 1. High level (working, studying or homeworking), 2. Intermediate (available) and 3. Low level (receiving welfare (pension or sick leave)).

*Psychopathology.* The OPCRIT diagnostic system was used to obtain ICD-10 diagnoses, based on
patient records and a Positive and Negative Symptom Scales (PANSS) interview (Kay et al., 1987). The latter was extended to include life-long symptoms (McGuffin et al., 1991). Seventeen PANSS interview videos and vignettes were randomly drawn and rated by the four raters (AMT, JEJ, MBP and CTL). For diagnoses there was an overall agreement of 82 % and a median kappa of 0.52. Control participants were screened with the Mini International Neuropsychiatric Interview (MINI) 6.0 for any prior and present psychiatric diagnoses (Sheehan et al., 2008: 0). MINI 6.0 was administered by the first author.

Premorbid and current functioning. The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was used for assessment of premorbid social and academic adjustment. The PAS has shown good validity and reliability (van Mastrigt and Addington, 2002). The social and academic parts of the scale have been found to be associated with different variables and is therefore recommended to be considered as independent factors (MacBeth and Gumley, 2008). The different PAS periods are childhood (0-11 years), early adolescence (12-15 years), late adolescence (16-18 years) and adulthood (19- years).

The Global Assessment of Functioning scale (GAF) was used to assess functioning the year prior to treatment entry and represents the best month of that year (Karterud et al., 1998; Pedersen et al., 2007). Reliability for GAF 1 year was based on 17 randomly drawn cases and gave an ICC(2,k) factor of 0.82 (0.60-0.93), which corresponds to excellent reliability (> .75) (Fleiss, 2011).

Ethics
All participants received oral and written information about the study. For the FEP participants, it was clearly stated that they could withdraw their consent at any time, and that participation did not impact their treatment. Control participants received DKK 400 equal to EURO 54 as compensation for their time and contribution. The protocol was submitted to the Regional Ethics Committee and pre-approval was found unnecessary as it only implicated questionnaires and interviews. The Data Protection Council, Region Zealand, approved data management (journal no. 12-000660).

Statistical analysis
All available data were included in the analyses. Frequency graphs for continuous measures were inspected visually to determine the approximation of the normal distribution and Levene’s test was used to determine equality of variance for group comparisons. The Student’s t-test and the Mann–Whitney U test were used for comparisons between the FEP and the control group. Spearman Rank
Correlation analyses were performed for all variables. All significance tests were two-tailed and the \( \alpha \)-level set at 0.05.

The K-Means cluster analysis was applied for the identification of groups based on premorbid social and academic change. The K-means cluster analysis seeks to create groups with minimal difference within groups relative to between groups (Dillon and Goldstein, 1984). As suggested by Larsen et al., the clusters were identified by change from childhood to the last PAS score, which was at least six months before psychosis onset. The ratings in childhood were labelled good (<1.50), intermediate (1.50–2.99) or poor (≥3.00), while the changes were labelled stable (<1.00), slightly deteriorating (1.00–1.99) and clearly deteriorating (>2.00) (Larsen et al., 2004). The change values were standardized for the modelling and there were no clear outliers. The best number of groups was based on the number of distinct patterns identified by the analyses, as suggested by (Larsen et al., 2004). It was three for the social PAS as a potential fourth group added a group between good stable and good deteriorating. It was four for the academic PAS.

One-way analysis of variance (ANOVA) and the Kruskal-Wallis test (for non-normal distributions of the number of adversities) was performed to test for differences between the groups on number of adversities. The IBM SPSS Statistics for Windows, Version 22.0 was used for all analyses.

Results

Premorbid trajectories and social factors

The K-mean cluster analyses identified three groups for social premorbid adjustment and four groups for academic. The social groups were 1. good stable (N=45), 2. good, clearly deteriorating (N=19) and 3. poor, slightly improving (N=16). The academic groups were 1. intermediate stable (N=38), 2. good, clearly deteriorating (N=11), 3. poor, clearly improving (N=4) and 4. good, slightly deteriorating (N=27). There were no statistically significant differences in the number of adversities between the FEP groups based on premorbid social adjustment (\( F(2,77) = 1.460, p = .24 \)) or premorbid academic adjustment (\( \chi^2(3, \ N = 80) = 4.46, p = .22 \)).

We included 101 (48 %) out of 198 eligible FEP participants, the reasons for which are presented in (Trauelsen et al., 2015). This paper had additional missing data for 21 people due to the premorbid adjustment: Fourteen had such an early onset of psychosis that no trajectory could be calculated and seven had incomplete data assessment. When combining those without PAS with those who were excluded, the remaining group (N=80) was one and half years younger (Mann-Whitney U 3750, p =
0.013), had fewer females (19% compared to 46%, $\chi^2 = 15.3, \ p < 0.01$) and more diagnoses of schizophrenia (93% compared to 70%, $\chi^2 = 18.2, \ p = 0.01$).

For both the FEP and the control group there were no associations between number of adversities and years of education ($r_s(100) = .05$ and $r_s(99) = -.07$), current occupational ($r_s(100) = .06$ and $r_s(99) = -.06$) and living status ($r_s(98) = .18$). In the FEP group, GAF function 1 year was negatively correlated to the number of childhood adversities ($r_s(97) = -.22, \ p = .04$) so that more adversities were related to worse functioning the year prior to treatment. The missing data here was due to incomplete data assessment.

See figures 1 and 2 and tables 2 and 3.

**Perceived support and family contact**

The FEP group reported lower rates of peer and adult support during childhood and adolescence than the control group ($p$-values < .001). Forty-four percent of the FEP group reported having had both peer and adult support compared to 88% of the control group, and 24% of the FEP group and 1% of the control group reported having had neither. Number of adversities was negatively correlated with adult support for both the FEP and the control group, while it only correlated negatively with peer support in the FEP group. When perceived support was adjusted for number of adversities, only peer support remained significantly lower in the FEP group. When number of adversities was adjusted for adult and peer support it remained significantly higher for the FEP group, but peer support diminished the risk caused by childhood adversities by 10%. There were no significant interactions between the number of adversities and perceived support. There was a negative correlation between number of adversities and face-to-face contact with a family member ($r_s(97) = -.23, \ p < 0.05$), but not telephone contact ($r_s(97) = -.19, \ NS$) in the FEP group. See tables 4 and 5.

**Discussion**

This study explored childhood adversities in relation to premorbid and current social factors and perceived support in a consecutive sample of people with non-affective FEP as compared to a matched control group. We hypothesized – but did not find – that those with worse premorbid trajectories had experienced more childhood adversities. Childhood adversity was not associated with occupational or living status or years of education. Lack of perceived peer support during
childhood and adolescence increased the risk of psychosis independent of childhood adversities and peer support diminished the risk of psychosis caused by childhood adversities. In addition, those with more childhood adversities had less current face-to-face contact with their family.

Premorbid trajectories and social outcome factors

We hypothesized but did not find that those with worse premorbid trajectories had experienced more childhood adversities. Our hypothesis was based on a few studies that found childhood adversity to be associated with worse premorbid adjustment in different premorbid time periods and on average (Conus et al., 2010; Schenkel et al., 2005; Stain et al., 2014) along with the rational consideration that severe adversity would decrease functioning. The most established theory, however is the neurodevelopmental, which considers premorbid deterioration to be a sign of decreasing brain function, which in turn is thought to be caused by genetic or biological factors. To explore this theory, we performed a post-hoc test to see if first-degree psychiatric illness was associated with deterioration. We found no differences between the groups based on social ($\chi^2(2, N = 70) = 2.81, p = .25$) and academic adjustment ($\chi^2(3, N = 69) = 1.83, p = .61$). Thus, both childhood adversities and familial risk were equally distributed across the identified trajectories, suggesting either a complex, or no relation between the factors. When considering how a person’s premorbid trajectory may change due to severe adversity this may not be surprising. There are several reasons why childhood adversity may not cause a deteriorating trajectory. The first is cessation of adversity, which could cause temporary functional improvement. This is supported by a longitudinal study by Kelleher et al. who found that the amount of psychotic experiences decreased in accordance with bullying and physical abuse (Kelleher et al., 2013). Other reasons include factors that could also improve functioning, such as the development of better coping mechanisms or the recognition of academic difficulties with an instigation of adequate assistance.

Our findings are in line with Stain et al.’s, who have provided the only comparable study by examining premorbid adjustment change between childhood and late adolescence (Stain et al., 2014). Change is comparable to our identified trajectories, except that it does not take age of onset into consideration. They found no differences in change between those with and without childhood adversity. This points towards a complicated relationship, and may even suggest that childhood adversities are not associated with trajectories.
As hypothesized, we found that having experienced more childhood adversities was associated with a lower level of global functioning. Global functioning represents the best consecutive month the year prior to treatment onset (average age 22 years) and thus differs from premorbid adjustment, which ends six months before the onset of psychotic symptoms (average age 17 years). Our results suggest that any functional effect of childhood adversity occurs only when the psychotic breakdown is occurring but not before. In addition to the few and mixed findings from previous studies (Addington et al., 2013; Duhig et al., 2015; Gil et al., 2009; Lysaker et al., 2001), our results suggest that further research is needed to establish whether childhood adversities predict worse global functioning in people with FEP.

The lack of associations between number of adversities and educational length, current occupational and living status was against our assumptions. The occupational status finding was similar to two studies (Campbell et al., 2013; Duhig et al., 2015) and dissimilar to two studies who found negative (Conus et al., 2010) and positive effects of childhood adversity (Spence et al., 2006). The dissimilarities may be due to study designs. Conus et al. was a file-audit study that included sexual and physical abuse, which makes their analysis very different from ours and their results less comparable. It is possible that their group with no sexual/physical abuse had been exposed to other childhood adversity, which could have given different results. Spence et al.’s group consisted of people with non-FEP and a mean age of 43 years who had been service-users for an average of 15 years. It is likely that occupational status was severely affected by the different interventions people had received, which again is very different from our study group. Thus, it may be that occupational status is not affected by childhood adversities in people with FEP.

With regards to living status, any effect of childhood adversities may have been overshadowed by previous institutionalization in childhood and adolescence. If a young person in Denmark is institutionalized at age 18 years, he/she has the right to receive comparable housing until the age of 23 years. This hypothesis is supported by a post hoc analysis that showed a significant correlation between living status and institutionalization ($r_s(95) = .35, p < .01$). It is also possible that any relation between childhood adversities and years of education were affected by the Danish social system, which highly prioritizes assistance to those with special needs and is considered to be equitable (Education Policy Outlook Highlights: Denmark - OECD, n.d.: 6; 16). In order to be certain that childhood adversities do not affect years of education, occupational and living status, more comprehensive and preferably longitudinal studies of non-affective FEP are needed.
Social support

Perceived peer and adult support during childhood and adolescence decreased the risk of psychosis and thus may add knowledge to our current models of psychosis. Half of the FEP group reported having had no peer support compared to 5% of the control group, which corresponds to an unadjusted 17 times (1/0.06) increased risk of psychosis by the lack of peer support. It means that half of the FEP group felt they had no peers to talk to about emotions and problems for the majority of their childhood and adolescence. Peer support alone remained a significant risk factor when childhood adversity was adjusted for, suggesting it is more independent of childhood adversity than adult support is. Peer support decreased the risk of psychosis caused by childhood adversities by 10%, while adult support did not change the risk. Thus, there was a buffering effect of having peer support during childhood and adolescence. Neither type of support interacted with childhood adversities. Peer support decreased the risk of psychosis caused by childhood adversities by 10%, while adult support did not change the risk. Thus, there was a buffering effect of having peer support during childhood and adolescence. Neither type of support interacted with childhood adversities. Thus, we did not find a diminishing effect of social support with increasing adversity severity, as it has been found for adult social support on trauma symptomatology and PTSD (Evans et al., 2013; Scarpa et al., 2006).

Adult support represented having any adult, within or outside the family, to talk to about problems and feelings. One third of the FEP group reported lack of adult support, compared to 8% of the control group, which corresponds to a 6 times (1/0.17) increased risk of psychosis by the lack of adult support. Children use their parents for support and most of the assessed adversities happened within the home-environment (Trauelsen et al. 2015), making it likely that these factors were associated. It may have been difficult to obtain support in an abusive and/or neglectful home environment (Jansen et al., Under review) and it is possible that there was a conceptual overlap between adult support and adversity. Adult support was correlated with number of adversities ($r_s(93) = -0.44, p < 0.01$). Of the CTQ subcategories, we found that emotional neglect had the highest association with adult support ($r_s(93) = -0.48, p < .01$) and that one of the questions regarding emotional neglect read “My family was a source of strength and support”. No other CTQ question directly concerned support, so the overlap could at most have represented a fifth of emotional neglect and none of the other subcategories. Thus, it seems that co-occurrence is the more likely explanation for the association between adversity and adult support. It may have represented a similar increase in feelings of hopelessness and social defeat as peer support. We have found no studies that examine perceived support and adversities during childhood and adolescence in people with psychosis, but an 18-month follow-up population study found that having a small primary
support group increased the risk of psychotic symptoms independent of adversity (Wiles et al., 2006). Peer support only correlated with one CTQ subcategory (emotional neglect \( r_s(92) = -0.26, p < .05 \)).

As hypothesized, those in the FEP group with more childhood adversities saw their family less at the time of treatment entry, suggesting that adversities may have affected these relationships. It is plausible that childhood adversity that have not been dealt with and may even still be happening to some degree makes it difficult to see the family. A qualitative study of our FEP group actually found that some mention that it can make them feel bad to spend time with their family (even though they love them) (Jansen et al., Under review).

**Strengths and limitations**

A cross-sectional and retrospective study design has certain limitations. Causal relationships are difficult to establish and recall bias are likely to occur. Recall bias could especially have affected premorbid adjustment, childhood adversities and perceived support in our study, as these factors represent the entire childhood. Studies have found that people with and without psychopathology, including psychosis, give equally valid and reliable reports, but that underreporting is very common (Fergusson et al., 2000; Fisher et al., 2011). Underreporting can both decrease the chance of finding associations and confound the actual findings.

We have previously discussed the effects of the differences between those who were included (52%) and excluded from the whole catchment area (Trauelsen et al., 2015). The approached group is thought to represent almost all cases of FEP in Region Zealand because of the Danish Health Service and our close contact with it, and we regard the FEP group representative of the catchment area even though 48% of the eligible participants were not included. Beyond our previous discussion (Trauelsen et al., 2015), we wish to mention that the low representation of women with PAS data could have decreased our chances of finding any differences between the premorbid trajectories, because women with psychosis report more childhood adversities than men (Fisher et al., 2009).

We did not include a comprehensive assessment of social factors in the current study. Possible important confounders include family poverty, IQ and cognitive and executive functioning (Campbell et al., 2013).

**Conclusion and implications**
Overall, childhood adversities were associated with global functioning the year prior to treatment, but neither to premorbid trajectories or social outcome factors. It would be preferable to examine these factors in longitudinal studies where resilience and risk factors can be assessed simultaneously and may be more closely examined. Both perceived support from peers and adults during childhood and adolescence was highly related to the risk of psychosis and adult support with the number of childhood adversities. Perceived support seems to be an area with great potential, especially with regards to prevention and early intervention. Since the family is a large part of the social network for people with FEP (Jolley et al., 2014), the association between childhood adversity and family contact may have clinical implications. We suggest that the assessment and treatment of childhood adversity should be included in the early intervention family work and that assistance is provided to increase the social networks of those who need it.

Acknowledgements
The authors would like to thank the interviewees and clinicians who contributed to the study.

Declaration of interest
None.

Funding
The study was supported by The Regional Health and Research Foundation, Zealand (AMT Grant number 12-000095); and The Lundbeck Foundation (AMT Grant number R93-A8804).

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Jansen JE, Pedersen MB, Trauelsen AM, et al. (Under review) Trauma and first-episode psychosis: Narratives of integration, coping and support.


Table 1. Socio-demographic and baseline data for persons with first-episode psychosis (N=101) and matched control persons (N=101)

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>FEP, n (%)</th>
<th>Controls, n (%)</th>
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<td>75 (74)</td>
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<tr>
<td>Female</td>
<td>26 (53)</td>
<td>26 (53)</td>
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<td><strong>Age, median (range)</strong></td>
<td>22.5 (18 – 34)</td>
<td>22 (18 – 33)</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Schizophrenia simplex</td>
<td>3 (3)</td>
<td></td>
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<tr>
<td>Schizoaffective psychosis</td>
<td>4 (4)</td>
<td></td>
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<tr>
<td>Unspecified</td>
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<tr>
<td><strong>Parental education</strong></td>
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<tr>
<td>No education</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td>3.19</td>
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<td>Lower skilled</td>
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<td>10 (10)</td>
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<tr>
<td>Higher skilled</td>
<td>38 (38)</td>
<td>40 (40)</td>
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<tr>
<td>Longer theoretical</td>
<td>28 (28)</td>
<td>28 (28)</td>
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<tr>
<td>Academic</td>
<td>7 (7)</td>
<td>13 (13)</td>
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<td></td>
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<tr>
<td><strong>Living status</strong></td>
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<tr>
<td>Independent</td>
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<td>101 (100)</td>
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<tr>
<td>Independent w. support</td>
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<tr>
<td>Institution</td>
<td>15 (15.20)</td>
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<tr>
<td>Without housing</td>
<td>2 (2.00)</td>
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<td><strong>Occupational status</strong></td>
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<td>72.93</td>
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<tr>
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<td>27 (27)</td>
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<tr>
<td>Working*</td>
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<td>Welfare*</td>
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<tr>
<td>Complete vocational education</td>
<td>16 (16)</td>
<td>25 (25)</td>
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<tr>
<td>Adult Support (FEP group N=93)</td>
<td>61 (66)</td>
<td>92 (92)</td>
<td>20.45</td>
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(Continued)
<table>
<thead>
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<th>Table 1. (Continued)</th>
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<tbody>
<tr>
<td><strong>Peer Support (FEP group N=92)</strong></td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td><strong>Number of adversities</strong></td>
</tr>
<tr>
<td><strong>Years of education</strong></td>
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<tr>
<td><strong>GAF 1 year (FEP group N=97)</strong></td>
</tr>
<tr>
<td><strong>Premorbid adjustment</strong></td>
</tr>
<tr>
<td>Social change</td>
</tr>
<tr>
<td>Academic change</td>
</tr>
<tr>
<td>Social level childhood</td>
</tr>
<tr>
<td>Academic level childhood</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test due to unequal variances or non-normal distribution.

* The highest parental vocational education.

* Fisher’s exact test.

* Including CTQ subcategories with moderate-severe cut-off scores, institutionalization and separation from primary caregivers.
Figure 1. Premorbid Adjustment Scale (PAS) trajectories for the social clusters (N = 80)

Figure 2. Premorbid Adjustment Scale (PAS) trajectories for the academic clusters (N = 80)
Table 2. Correlations between premorbid adjustment, childhood adversities and social outcome factors in the FEP group (N = 72-101)

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<td>2</td>
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<td>-.439&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>.407&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>-233&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>.430&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>9</td>
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<td>.157</td>
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<td>-.242&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>-.087</td>
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<td>.239&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>.001</td>
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<td>.024</td>
<td>-.093</td>
<td>.092</td>
<td>.041</td>
<td>.063</td>
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</tbody>
</table>

Notes: Spearman Rank Correlations.
<sup>a</sup> Keep in mind that positive premorbid scores represent worse adjustment.
<sup>b</sup> Talking on the phone
<sup>c</sup> Reported psychosis, bipolar, autism and depression in first degree relatives.
<sup>*</sup> Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).
Table 3. Associations between childhood adversities and social factors in the control group (N = 93-101)

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<td>.052</td>
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<td>- .069</td>
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<td>.074</td>
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<tr>
<td>5.</td>
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<td>.063</td>
<td>- .069</td>
<td>.151</td>
<td>.074</td>
<td>1.000</td>
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<td>.132</td>
<td>.006</td>
<td>- .033</td>
<td>- .246&lt;sup&gt;**&lt;/sup&gt;</td>
<td>.021</td>
<td>1.000</td>
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</tbody>
</table>

Notes: Spearman Rank Correlations.
<sup>a</sup> Everyone lived independently.
<sup>b</sup> Reported psychosis, bipolar, autism and depression in first degree relatives.
* Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).
### Table 4. Number of adversities in the groups based on social premorbid adjustment (PAS) change (N=80) and on academic premorbid adjustment (PAS) change (N=81)

<table>
<thead>
<tr>
<th>PAS Social</th>
<th>1 Good stable (N=45)</th>
<th>2 Good deteriorating (N=19)</th>
<th>3 Poor, slightly improving (N=16)</th>
<th>Mean Square between groups</th>
<th>F(2, 77)</th>
<th>p=</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adversities a</td>
<td>2.93 (1.94)</td>
<td>2.47 (1.78)</td>
<td>2.06 (1.53)</td>
<td>4.860</td>
<td>1.46</td>
<td>.24</td>
<td>0.20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PAS academic</th>
<th>1 Intermediate stable (N=38)</th>
<th>2 Good, clearly deteriorating (N=11)</th>
<th>3 Poor, clearly improving (N=4)</th>
<th>4 Good, slightly deteriorating (N=27)</th>
<th>χ²(df=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adversities b</td>
<td>2.95 (1.89)</td>
<td>3.27 (2.57)</td>
<td>1.50 (1.00)</td>
<td>2.26 (1.35)</td>
<td>4.46</td>
</tr>
</tbody>
</table>

*Analysis of variance.
*Kruskal-Wallis test.

### Table 5. Perceived support during childhood and childhood adversities on risk of psychosis in persons with FEP (N=92/93) and non-clinical control persons (N=100)

<table>
<thead>
<tr>
<th>Support</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR a</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
<th>OR b</th>
<th>95 CI</th>
<th>p-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer support</td>
<td>61 (65.60)</td>
<td>92 (92)</td>
<td>0.06</td>
<td>0.02-0.15</td>
<td>&lt;0.001</td>
<td>31.47</td>
<td>0.12</td>
<td>0.04-0.36</td>
<td>&lt;0.001</td>
<td>14.10</td>
</tr>
<tr>
<td>Adult support</td>
<td>47 (51.10)</td>
<td>95 (95)</td>
<td>0.17</td>
<td>0.07-0.41</td>
<td>&lt;0.001</td>
<td>15.60</td>
<td>0.82</td>
<td>0.27-2.52</td>
<td>0.725</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of adversities, mean (SD)</td>
<td>2.87 (1.98)</td>
<td>0.65 (1.13)</td>
<td>2.56</td>
<td>1.91-3.42</td>
<td>&lt;0.001</td>
<td>40.18</td>
<td>2.64</td>
<td>1.85-3.76</td>
<td>&lt;0.001</td>
<td>28.48</td>
</tr>
<tr>
<td>Number of adversities, mean (SD)</td>
<td>2.30 d</td>
<td>1.63-3.24</td>
<td>&lt;0.001</td>
<td>22.38</td>
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</table>

*OR, Odd ratio; CI, confidence interval
*a Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education
*b Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and number of adversities
*c Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and adult support
*d Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and highest parental education and peer support
Paper 3

Metacognition in first-episode psychosis and its association with positive and negative symptom profiles

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\textsuperscript{**} This paper is part of the OPUS Zealand research project: Family Intervention in First-episode Psychosis. An investigation of metacognition, expressed emotion and caregiver experiences. From January 1, 2012 the project has the following research group: Erik Simonsen, MD, PhD (PI). Ulrik Haahr, MD (PI). Christopher Høier Trier, MSc in Psychology. Marlene Buch Pedersen, MSc in Psychology. Hanne-Grethe Lyse Nielsen, RN. Mette Sjoestroem Petersen, MA (ed) in Educational Psychology, Jens Einar Jansen, PhD. Ulf Soegaard, MD. Anne Marie Trauelsen, MD. From September 1. 2014 Signe Dunker Svendsen, RN. From Psychiatric Research Unit, Psychiatry Region Zealand, Denmark. Early Psychosis Intervention Center, Psychiatry East Region Zealand, Denmark.
ABSTRACT

There is growing evidence that the ability to synthesize knowledge regarding mental states in self and others and use this ability to solve problems (metacognition) is impaired in non-affective psychosis and associated with positive and negative symptom severity. We sought to (a) investigate the severity of metacognitive impairments in first-episode psychosis (FEP) compared to well-matched non-clinical controls and (b) explore associations with positive and negative symptom profiles. Ninety-seven people with FEP were compared to 101 control persons. Metacognition was assessed with semi-structured interviews and the Metacognitive assessment scale-abbreviated. Four groups based on positive and negative symptoms were identified by cluster analysis and compared on metacognition, childhood adversities, DUP and premorbid social and academic adjustment. Those with high levels of negative symptoms had poorer metacognitive abilities. Those with high positive and low negative symptoms did not have poorer metacognitive abilities than those with low positive and negative symptoms. None of the other predictors differed between the symptom groups. The FEP group had poorer metacognitive abilities than the control group. Inclusion of metacognition in psychosis models may improve our understanding of negative symptoms, while previous findings of a relation with positive symptoms may have been confounded. Implications for current interventions are discussed.

**Keywords:** Case-control; risk; positive symptoms; negative symptoms; self-reflectivity; mentalizing.
1. Introduction

There is accumulating evidence that metacognition may be an important predictor of positive and negative symptoms in addition to established predictors in people with non-affective psychosis (Hamm et al., 2012; McLeod et al., 2014). Metacognition is concerned with how individuals make sense of their own and others’ behaviour in terms of mental states and the utilisation of this capacity to solve problems and cope with mental states, which cause distress (Semerari et al., 2003; Lysaker et al., 2005, 2013). Metacognition is related to theory of mind (ToM), which concerns the ability to attribute mental states such as thoughts, intentions and beliefs to oneself and others and to recognize that other’s mental states can differ from one’s own and from reality (Brüne, 2005; Sprong et al., 2007). There is also evidence that impairments in metacognition are greater in those diagnosed with non-affective psychosis compared to controls with significant medical adversity (HIV) (Lysaker et al., 2011b) and that metacognition is a predictor of non-affective psychosis (FEP) (Lysaker et al., 2014). With the exception of three studies (Macbeth et al., 2014; McLeod et al., 2014; Vohs et al., 2014), studies exploring metacognition have largely concerned participants with prolonged non-affective psychosis. Vohs et al. (2014) found that people with a FEP had lower metacognitive abilities compared to those with prolonged psychosis and psychiatric controls. The authors noted that sample sizes were small and thus generalizability to the larger population was limited. The other studies did not include control groups. Such a comparison is important to establish the nature and extent of metacognitive difficulties in people with FEP.

Several studies have established that metacognition is associated with negative symptoms in people with prolonged psychosis (Lysaker et al., 2005; Hamm et al., 2012; Nicolò et al., 2012; Rabin et al., 2014; Vohs et al., 2014) and a few have shown it in people with FEP (Macbeth et al., 2014; McLeod et al., 2014; Vohs et al., 2014). Six studies found correlations between negative symptoms and metacognition (Lysaker et al., 2005; Hamm et al., 2012; Nicolò et al., 2012; Macbeth et al., 2014; McLeod et al., 2014; Rabin et al., 2014; Vohs et al., 2014). In addition, Hamm et al. (2012) found that metacognition at baseline predicted the level of negative symptoms six months later and McLeod et al. (2014) found that metacognition increased the prediction of recovery of negative symptoms after six and 12 months controlling for baseline symptom severity, duration of untreated psychosis and premorbid adjustment. With regards to associations between metacognition and positive symptoms, the results are less consistent. Three studies found no correlations with metacognition (Nicolò et al., 2012; Macbeth et al., 2014; Vohs et al., 2014), while two studies
found fewer correlations with positive than negative symptoms (Lysaker et al., 2005; McLeod et al., 2014). Hamm et al. (2012) found that metacognition correlated with positive symptoms, but that metacognition did not predict positive symptoms at six months follow-up. McLeod et al. (2014) found that metacognition at baseline also predicted positive symptoms at six and 12 months follow-up. Importantly, many of these studies have methodological issues, which may have contributed to the lack of findings. For example, MacBeth et al. (2014) had a small sample size (N=34) and their FEP sample had low levels of positive symptoms, with an average PANSS score for positive symptoms of 10.11 (SD 5.6), which may have made it difficult to find any associations. Nicolò et al. (2012) had a small sample size (N=45) that included only stable (no recent hospitalizations) outpatients without substance abuse, which may also have rendered associations hard to find. In addition to these limitations, just one study (McLeod et al., 2014) included the established predictors of positive and negative symptoms. These include duration of untreated psychosis (DUP) (Crumlish et al., 2009; White et al., 2009; Boonstra et al., 2012), premorbid social and academic adjustment (PAS) (MacBeth and Gumley, 2008; Simonsen et al., 2010; Chang et al., 2013) and less certainly childhood adversity (Bentall et al., 2012; Sitko et al., 2014; van Nierop et al., 2014; Trotta et al., 2015). Childhood adversities have been found to predict the presence of positive symptoms (Bentall et al., 2012; Sitko et al., 2014; van Nierop et al., 2014; Duhig et al., 2015) and a recent meta-analysis has concluded that childhood adversities increase the risk of persistence of psychotic experiences in both clinical and non-clinical populations (Trotta et al., 2015). Thus, prevailing studies have not been representative of non-affective FEP populations. In addition to these studies, a review showed that ToM more often associated with negative than positive symptoms (Harrington et al., 2005), while a meta-analysis found that facial emotion perception was related to both negative and positive symptoms (Kohler et al., 2010). The mixed findings of the associations between metacognition and positive symptoms emphasize the continued need for research to explore them. One possible explanation for the mixed findings is that found relations between metacognition and positive symptoms have been confounded by the presence of negative symptoms. It has not been sufficiently researched how metacognitive abilities differ in relation to both positive and negative symptoms independently and together. Studies on metacognition have explored associations with positive and negative symptoms separately (Hamm et al., 2012; Nicolò et al., 2012; Macbeth et al., 2014; McLeod et al., 2014) and not taken into account the possibility of their co-occurrence. In addition, only one of the above-mentioned studies and no other FEP studies
have compared the levels of metacognition in their samples to non-clinical control groups (Rabin et al., 2014), albeit it is the foundation of this research.

1.2. Aims and hypotheses

Therefore, we aimed to conduct a study exploring the association between metacognition and positive and negative symptoms in non-affective FEP. We wished to improve on previous studies by controlling for established predictors of positive and negative symptoms. Building upon the methodology of Buck and colleagues (2014) we wished to identify positive and negative symptom profiles in people with FEP (Buck et al., 2014). In addition, we wished to compare the levels of metacognition in people with non-affective FEP to a well-matched non-clinical control group to establish whether metacognition as measured with the Metacognitive assessment scale-abbreviated is lower for people with FEP. We hypothesized that:

i. Metacognitive abilities would be lower for people with non-affective FEP than for the non-clinical control group.

ii. We would identify 4 clusters of positive and negative symptoms (High Negative/Low Positive; High Negative/ High Positive; Low negative/ High Positive and Low positive/Low Negative)

iii. Poorer metacognitive abilities would be associated with high levels of positive and negative symptoms independently and together.

2. Methods

2.1. Participants

2.1.1. FEP group

The sample has previously been described by Trauelsen et al. (2015). Denmark has a nationwide out-patient, early intervention programme (OPUS) for people with FEP (Petersen et al., 2005). Inclusion criteria for OPUS during the study were an ICD-10 diagnosis F20-29, except F21, and an age of 18-35 years. Exclusion criteria were a previous diagnosis of non-affective psychosis. The catchment area was Region Zealand (population = 816,359) and everyone included in treatment between April 1 2011 and April 1 2013 was approached for participation. Additional criteria for the study were sufficient Danish skills to complete the interviews. The FEP participants were assessed as soon as possible, but the median time from treatment start to assessment was 94 days (range 456 days). Forty-one percent were psychotic in the week prior to either the first or second interview,
when the PANSS was performed.

2.1.2. Control group
Inclusion criteria were living in the catchment area and being 17 to 34 years of age. Exclusion criteria were previous or current psychiatric disorders and insufficient Danish skills to complete the interview. Control persons were matched 1:1 by gender, age (+/-1 year), and parental education (+/-1 one on a 5-point scale). Control persons were recruited through advertisements in newspapers, at educational institutions, libraries, sport clubs and by word of mouth. They were included from October 1 2013 to May 22 2014.

2.2. Measures
2.2.1. Indiana psychiatric illness interview (IPII)
The IPII is a semi-structured interview where the interviewees are asked to talk about their life. This includes their life story; the psychiatric problems that they may or may not think they have, and how they have been affected by them; how they control and are controlled by these problems; how they are affected by and affect other people; and how their future will be (Lysaker et al., 2002). The control participants go through the same line of questioning, but instead of psychiatric problems, they are asked about psychological difficulties that have occurred within the last two years. The interview is conversational with minimal amount of direction, allowing for a spontaneous narrative. The interview lasts about 30 minutes, and the responses are audio taped and subsequently transcribed. To minimize the interviewer’s influence on the interviewee, the IPII was the first interview to be performed for both participant groups.

2.2.2. Metacognition assessment scale-abbreviated (MAS-A)
MAS-A (Lysaker et al., 2005) is an elaboration of the metacognition assessment scale (MAS) which was developed for metacognitive assessment in psychotherapy (Semerari et al., 2003). The MAS-A brings a dimensional structure to the original MAS and demands a presence of lower order metacognitive skills before the highest scores are awarded. The ratings were based on the IPII transcripts and thus measured the presence of observations and elaborations conveyed by the interviewees.
The MAS-A consists of the four subscales Self-reflectivity, Awareness of the Mind of the Other (AoM), Decentration and Mastery. Self-reflectivity consists of nine levels, which range from
identifying to integrating knowledge about oneself with the identification of affective and cognitive operations as a benchmark for achieving higher ratings. AoM consists of seven levels, which range from identifying to integrating knowledge about others, in a progressively more complex way. Decentration consists of three levels. It reflects a person’s ability to understand that other people lead their lives and interact with each other independent of the person. Mastery consists of nine levels and concerns the ability to use understanding of self and others to solve or overcome psychological difficulties. The MAS-A total score is the sum of the four subscales.

The MAS-A has been found to have good inter-rater reliability with intra-class coefficients ranging from 0.71 to 0.91 (Lysaker et al., 2005). The current study calculated reliability for 20 % randomly drawn IPPI transcripts rated by the first and third author. Cronbach’s alpha was 0.87 for the control group and 0.88 for the FEP group.

2.2.3. Childhood adversities
The Childhood Trauma Questionnaire (CTQ) was used for trauma assessment (Bernstein et al., 2003). We used the Danish validated version (Bernstein and Fink, 2011). The CTQ consists of five subcategories, each represented by five questions. The CTQ subcategories were dichotomized using the cut-off scores from moderate to severe as suggested by Bernstein et al. (Bernstein and Fink, 2011). Separation and institutionalization were assessed with the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Smith et al., 2002; Bifulco et al., 2005). The number of adversities ranged from zero to seven and was calculated by combining the five CTQ subcategories with separation and institutionalization.

2.2.4. Psychopathology
The OPCRIT diagnostic system was used to obtain ICD-10 diagnoses, based on patient records and a Positive and Negative Symptom Scales (PANSS) interview (Kay et al., 1987). The latter was extended to include life-long symptoms (McGuffin et al., 1991). For analyses, we used the five factor categorization suggested and validated by van der Gaag (2006). A psychologist or medical doctor, i.e. AMT, JEJ, CHT or MBP, administered the instruments and had all received training by a senior psychiatrist. Control participants were screened with the Mini International Neuropsychiatric Interview (MINI) 6.0 for any prior and present psychiatric diagnoses (Sheehan et al., 2008, p. 0). MINI 6.0 was administered by the first author.

2.2.5. Duration of untreated psychosis and premorbid adjustment
DUP was defined as having a psychotic symptom score equal to or above 4 for the whole day a week in a row or several times a week for several weeks, as described by (Melle et al., 2006). Any periods without symptoms were subtracted from the DUP. The DUP was considered over when antipsychotic medication, OPUS or inpatient treatment started. Any uncertainties regarding DUP ratings were resolved between the authors and information drawn from electronic patient files and staff. Test–retest reliability for this method of determining DUP from is reported as good (intraclass coefficient $r = .96, p < 0.01$) (Larsen et al., 1998).

The Premorbid Adjustment Scale (Cannon-Spoor et al., 1982) was used for assessment of premorbid social and academic adjustment. The PAS has shown good validity and reliability (van Maastrigt and Addington, 2002). The median score for all eligible periods were presented separately for social and academic adjustment, as suggested by (MacBeth and Gumley, 2008). Seventeen PANSS interview videos and vignettes were randomly drawn and rated by the four raters. For diagnoses, there was an overall agreement of 82 % and a median kappa of 0.52. The ICC (2, k) coefficients for DUP was 0.94. For the PANSS van der Gaag components, the ICC (2, k) coefficients were: Positive component score 0.81, negative component score 0.90, depressive component score 0.86, excitement component score 0.64 and cognitive component score 0.81. These numbers represent excellent >.75 and fair-to-good reliability 0.40-0.75 (Fleiss, 2011).

2.2.5. Demographic data
Parental education was defined as the highest educational degree achieved by either parent with whom the patient had lived. We wished to match on this parameter to avoid confounding, as parental education is associated with increased risk of childhood adversity and increased risk of psychosis (Croudace et al., 2000; Sidebotham and Heron, 2006). Lower skilled referred to education that required special training, usually with participation in long-term (> 2 years) courses. Higher skilled referred to theoretical-practical education of about 4 years with an emphasis on the practical. Longer theoretical referred to education of about 4 years with an emphasis on the theoretical. Academic referred to having a University Degree.

2.3. Ethics
All participants received oral and written study information. For persons with FEP, it was clearly stated that they could withdraw their consent at any time and that participation had no impact on their treatment. Control persons received DKK 400 equal to EURO 54 as compensation for their
time and contribution. The protocol was submitted to the Regional Ethics Committee and pre-
approval was found unnecessary. The Data Protection Council, Region Zealand, approved data
management (journal no. 12-000660).

2.4. Statistical analysis
The IBM SPSS Statistics for Windows, Version 22.0 was used for all analysis.
Frequency graphs of continuous measures were inspected visually to determine approximation of
the normal distribution. T-tests were performed to compare variables between the FEP and the
control group. PAS social and DUP were transformed by logarithmic functions due to skewed
distributions securing good enough normality distribution within groups for all variables. If the
variable was not continuous or normally distributed, as for age, a non-parametric test was
performed.
The K-Means cluster analysis was applied for the identification of four groups based on positive
and negative symptom z-scores. Two outliers were excluded from the cluster analysis, as they were
too influential; they were allocated to their subgroups subsequently (Steinley, 2006). The groups
were derived based on distribution which secures a minimal within-groups difference relative to the
between-groups difference (Dillon and Goldstein, 1984). The groups were labelled in
correspondence with their values as 1) Low Positive/Low Negative; 2) High Positive/Low
Negative; 3) Low Positive/High Negative and 4) High Positive/High Negative. Before performing a
one-way multivariate analysis of variance (MANOVA) to test for differences between the groups,
correlation analyses were performed. The MANOVA was performed to compare the groups on
metacognition, number of adversities, DUP and premorbid social and academic adjustment.
Multicollinearity was not an issue with the generally low correlations. See supplementary table 1.
The Hosmer-Lemeshow goodness-of-fit tests were non-significant and variances were therefore
assumed equal. Based on the Box’s M value of 29.14 and associated value of 0.99 the covariance
matrices between the groups were also assumed to be equal for the purposes of the MANOVA
(Tinsley and Brown, 2000). We chose Pillai’s trace as it is the least sensitive to violations of
assumptions. Subsequently, the Fisher’s Least Squared Difference method was applied for a series
of post-hoc analyses for individual mean difference comparisons across all four groups and the five
dependent variables.

3. Results
3.1. Descriptive data

There were 194 eligible persons with FEP, of which 101 (52%) fully consented to participate. Exclusions were due to lack of a wish to participate (51); inability to obtain contact (18); withdrawal of consent (14); inclusion before the CTQ was included in the study protocol (11) and insufficient Danish skills (3).

This paper contained additional missing data for the 101 included FEP participants. These were due to a lack of PAS data because of very early onset of psychosis (N=2); lack of DUP due to schizophrenia simplex (F20.6) (N=3) and partially missing data due to incomplete data assessment (N=13). Thus, 83 persons had full datasets and were included in the symptom profile comparisons. Four of the 101 participants with FEP had missing metacognitive data. Therefore, 97 persons were compared to the control group on metacognition. They did not differ from the excluded group in relation to age (Mann-Whitney U 4160, p = 0.065) but held fewer females (43 % compared to 26 %, $\chi^2 = 5.42$, $p = 0.02$) and more people with schizophrenia (68 % compared to 92 %, $\chi^2 = 24.6$, $p < 0.000$).

3.2. Case control comparisons

All the metacognitive subscales were significantly lower in the FEP group with the largest difference for Self-reflection ($z$-score = 5.29, $p <0.001$) and the lowest for AoM ($z$-score= 4.37, $p <0.001$). The number of adversities was significantly higher in the FEP group with an average of 2.87 adversities compared to 0.65 adversities in the control group ($p < 0.001$). The details of the adversities are presented in Trauelsen et al. (2015). Demographic and clinical characteristics are presented in Table 1.

3.3. Cluster analysis

The K-means cluster analysis identified four symptom profiles. Group 1 had Low Positive/Low Negative symptoms; positive mean score (van der Gaag) 8.82 (SD 1.88) and negative mean score 12.44 (SD 3.07). Group 2 had High Positive/Low Negative); positive mean 16.21 (SD 2.72) and negative mean 10.71 (SD 2.09). Group 3 had Low Positive/High Negative); positive mean 8.17 (SD 2.17) and negative mean 24.75 (SD 3.14). Group 4 had High Positive/High Negative); positive mean 16.30 (SD 3.60) and negative mean 19.48 (SD 3.57).

3.4. Symptom profile comparisons
There was a significant difference between the symptom groups for the MANOVA including premorbid adjustment, DUP, metacognition and number of adversities between (Pillais’ Trace = .42, F(15, 231) = 2.51, p = .002). The effect size, Partial Eta Squared, was 0.14, which implies that 14% of the variance in the shared constructed dependent variable (canonically derived) was accounted for by positive and negative symptom severity. To determine which dependent variables had the greatest MANOVA effect the standardized discriminant function coefficients were calculated. They suggested that the symptom groups were maximally differentiated by a canonical variable with greatest weight from the MAS-A total score (0.96), followed by DUP (0.54) and premorbid social adjustment (-0.44). This corresponded with the correlations between the dependent variables and the canonically derived scores which were 0.80 for the MAS-A total score and 0.27 for DUP, and smaller than ±0.10 for the last three variables.

The post-hoc analyses showed that the MAS-A total score differed significantly between the groups (p < 0.001). The groups with high negative symptom scores had lower MAS-A total scores than the groups without, showing an independent relation between metacognition and negative symptoms. On the contrary, the group with high positive symptoms and low negative symptoms did not have significantly lower MAS-A total than the group with low positive and negative symptom scores. The correlations between MAS-A subscales and positive symptoms were all insignificant (r = -0.14 to -0.03), whereas those with negative symptoms were all significant (r = -0.29 to -0.415). The DUP trended towards significance (p = 0.06) reflecting that the groups with high positive symptom scores had longer DUPs than the groups without, independent of negative symptom scores. The correlation analyses, MANOVA and post-hoc analyses are presented in tables 2 - 4.

3.5. Post-hoc symptom group comparisons of metacognitive subscales

The MAS-A total score was the only variable that differed significantly between the groups. Therefore, and in addition to our original hypotheses, we explored whether these differences were due to any particular MAS-A subscale. A MANOVA analysis could not be conducted due to unequal variances between the groups (Levene’s Test of Equality of Error Variances for AoM was F(3, 90) = 3.71, p = 0.01 and F(3, 90) = 4.79, p = 0.004 for Mastery). The non-parametric Kruskal-Wallis test was performed instead and showed significant differences between the groups on Self-reflectivity (\(\chi^2 = 16.73, p = 0.001\)); Decentration (\(\chi^2 = 10.75, p = 0.01\)); and Mastery (\(\chi^2 = 17.80, p = 0.01\)). These results were followed by non-parametric Mann-Whitney U tests between the
individual groups. Bonferroni corrections were applied for each scale, which consisted of six analyses. Overall, Self-reflectivity (0.001), Decentration (0.006) and Mastery (0.002) scores were all higher in the Low Positive/Low Negative group compared to the Low Positive/High Negative group. The Low Positive/Low Negative group was higher than the High Positive/High Negative group on Self-reflectivity (0.001) and Mastery (< 0.001). Of note, the subscale comparisons were based on larger groups than for the MANOVA since the variables with missing data (DUP, PAS and PANSS) were not included in these post-hoc analyses.

4. Discussion

We found significantly lower levels of metacognition in participants with FEP compared with age, gender and parental education matched non-clinical controls. As we predicted we identified four clusters of positive and negative symptoms (High Negative/Low Positive; High Negative/High Positive; Low negative/High Positive and Low positive/Low Negative). Based on this cluster analysis we found that impairments in metacognition were only noted in those subgroups with higher negative symptoms. Post-hoc analyses revealed that these findings were due to differences in the metacognitive subscales Self-reflectivity, Decentration and Mastery. There were no differences between the symptom profiles on DUP, premorbid adjustment or number of childhood adversities.

Therefore, the findings of this study suggest that impairments in metacognitive abilities are associated with negative symptoms independent of the level of positive symptoms, while there was no consistent association between metacognition and positive symptoms. This corresponds with the existing literature that show mixed findings of the relation between metacognition and positive symptoms and consistent findings for negative symptoms (Lysaker et al., 2005; Hamm et al., 2012; Nicolò et al., 2012; Macbeth et al., 2014; McLeod et al., 2014). An important difference in our study is that the groups with either high positive or high negative symptoms were protected from confounding by the other symptom. For example, McLeod et al. (2014) found no correlation between metacognition and positive symptoms, but found that metacognition increased the prediction of positive symptoms at follow-up. The model was not adjusted for negative symptoms and thus may have been confounded by them. Others have found a correlation between metacognition and positive symptoms, but no association in a following regression model, again suggesting that findings may have been confounded (Hamm et al., 2012). Our findings suggest that
metacognition does not affect the level of positive symptoms, and we strongly encourage researchers to replicate our finding or adjusting for negative symptoms when exploring this relation. The strong relation between metacognition and negative symptom severity also corresponds well with the literature (Lysaker et al., 2011a; Hamm et al., 2012; Nicolò et al., 2012; Macbeth et al., 2014; Rabin et al., 2014; Vohs et al., 2014). The only unexpected finding was that AoM was not poorer for the High Negative groups ($p = 0.10$). As there was a significant negative correlation between AoM and negative symptoms in the whole group ($r = -0.327$) this could be due to a low power to detect the relationship as the group with the highest negative symptom score (high neg/low pos) was small ($n=12$).

The levels of metacognitive abilities were in line with the largest FEP sample (McLeod et al., 2014) and the non-clinical control group was similar to the non-clinical control group in a case-control study of people with depression (Ladegaard et al., 2014). However, two studies with smaller FEP sample sizes found lower metacognitive levels on some of the MAS-A subscales (Macbeth et al., 2014; Vohs et al., 2014). Macbeth et al. (2014) found that AoM and not Self-reflectivity was impaired and suggested this might apply to all FEP groups. Our analyses suggested otherwise as we found almost equal differences for all the metacognitive subscales ($z = -5.29$ to $-4.37$). The two studies had small sample sizes, which might explain the different results ($N = 34$ and $26$).

We found a trend towards significance for between-group differences for DUP, but none for number of adversities or premorbid adjustment. The lack of associations may be due to the three-month time-period from service entry to assessment where symptom severity should have improved due to instatement of antipsychotic treatment (Lewis et al., 2002). This may have lowered symptom severity and thereby made it more difficult to detect differences. It was unexpected that DUP was not longer for the Low Positive/High Negative group, as meta-analytic evidence have associated DUP with negative symptom severity (Marshall et al., 2005; Perkins et al., 2005; Boonstra et al., 2012). Our results suggest that metacognition is a stronger predictor of negative symptoms than DUP and PAS, and that DUP is a stronger predictor of positive symptoms. This is indicative of independence between DUP, PAS and metacognition and suggests they contribute to different aspects of psychosis. Therefore, we recommend that metacognition is included in etiopathological and recovery models of psychosis and be considered as a target for interventions as suggested by Lysaker et al (Lysaker and Dimaggio, 2014). The lack of association between childhood adversities
and symptom profiles implies that childhood adversity is unimportant for the level of symptoms in people with FEP. The findings from other FEP studies are mixed, but mostly they find no or weak associations; one study found no correlation between total adversity scores and positive or negative symptoms (Ramsay et al., 2011), while another found a weak correlation with positive and none with negative symptoms (Duhig et al., 2015) and a third found correlations between total adversity score and positive but not negative symptoms (Ucok A. and Bikmaz S., 2007). All studies used the CTQ. No reviews have examined the associations in FEP samples, but Trotta et al.’s (2015) meta-analysis of psychotic experiences found that childhood adversities increased the risk of their persistence in both clinical and non-clinical populations. Thus, the associations may change in the different phases of psychosis. It is possible that the association with childhood adversities is overshadowed by other factors in the acute first phase of psychosis. These questions require further examination.

4.1 Strengths and limitations

The cross-sectional design does not allow for causal inferences. It is therefore possible that interview performance was affected by negative symptom severity resulting in lower metacognitive scores and not vice versa. The timing of assessment is another weakness as especially positive symptom severity may have been affected by early treatment response (Lewis et al., 2002). Blinding was not applied to the ratings of metacognition, which can have biased the results, most likely in the direction of lowered scores for persons with psychosis and higher for control persons. We did not assess intelligence or executive function, which is considered a minor weakness as metacognition is largely found to be an independent quality (Sprong et al., 2007; Koelkebeck et al., 2010; Brüne et al., 2011). Recall bias are inevitable in retrospective assessment, but studies have demonstrated that recall of adversities are reasonably stable in people with FEP (Fisher et al., 2011) and that they are comparable to people without psychopathology (Fergusson et al., 2000). However, 20 % of the sample was randomly picked after finished rating to ensure reliability and validity. The MAS-A raters calibrated their rating skills with the Lysaker research group. Also, their internal reliability was found satisfactory for the applied statistical analyses. The organization of the Danish Health Service ensures that almost all cases of first-episode psychosis are referred to the early intervention service. We therefore regard the FEP group representative of the catchment area even though half of the eligible group was not included. The current study is one of the largest to examine metacognition by the MAS-A in a FEP group and compare it with a well-matched control.
4.2. Future research and clinical implications

The strong association between the high negative symptom groups and metacognition conveys both clinical and research implications. It signifies that especially those with high levels of negative symptoms have difficulties recognizing and formulating their inner states. This could impede communication of mental states with the service, such as asking for help when dealing with disturbing inner states. At the same time, the clinicians may find it difficult to understand and attune to the service user if this information is inaccessible. Consequently, it may be harder to tailor and adjust interventions for this group. Explicit assessment of metacognitive difficulties for those with high negative symptom levels might improve both the service users’ and the clinicians’ recognition of this possible barrier to treatment and serve as a starting point for metacognitive improvements.

We suggest future studies examine whether metacognitive improvements decrease the level of negative symptoms, both to establish the association that we have found and to develop interventions that can diminish the negative symptoms. This is supported by the findings that metacognitive development is dependent upon social interactions (Yagmurlu et al., 2005; Colvert et al., 2008; Ontai and Thompson, 2008) and that negative symptoms have been found to improve with improved social environment (Wing and Brown, 1970).

4.3. Financial support

The study was supported by The Regional Health and Research Foundation, Zealand (A.M.T. Grant number 12-000095); and The Lundbeck Foundation (A.M.T. Grant number R93-A8804).

4.4. Conflict of interest

None.

Acknowledgements

We are grateful for the time and effort that the interviewees and clinicians have put into the study and for the supervision and collaboration provided by Professor Paul Lysaker and his research group.

References


Table 1. Demographic and clinical data for persons with first-episode psychosis (n=101) and matched control persons (n=101)

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<td>University/completed vocational education</td>
<td>14 (14)</td>
<td>25 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental education&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No education</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td>3.19</td>
<td>0.527</td>
</tr>
<tr>
<td>Lower skilled</td>
<td>14 (14)</td>
<td>10 (10)</td>
<td></td>
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<tr>
<td>Higher skilled</td>
<td>38 (38)</td>
<td>40 (40)</td>
<td></td>
<td></td>
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<tr>
<td>Longer theoretical</td>
<td>28 (28)</td>
<td>28 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>7 (7)</td>
<td>13 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of adversities&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.87 (1.98)</td>
<td>0.65 (1.13)</td>
<td>Z= -8.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metacognition (MAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reflectivity (N= 97)</td>
<td>5.24 (1.50)</td>
<td>5.00 (5.50)</td>
<td>6.33 (1.21)</td>
<td>6.50 (5.00)</td>
</tr>
<tr>
<td>AoM (N= 97)</td>
<td>3.42 (0.95)</td>
<td>3.00 (5.00)</td>
<td>4.02 (0.98)</td>
<td>4.00 (5.00)</td>
</tr>
<tr>
<td>Decentration (N= 97)</td>
<td>1.20 (0.62)</td>
<td>1.00 (3.00)</td>
<td>1.65 (0.59)</td>
<td>1.50 (4.50)</td>
</tr>
<tr>
<td>Mastery (N= 97)</td>
<td>4.74 (1.47)</td>
<td>5.00 (7.00)</td>
<td>5.68 (1.09)</td>
<td>6.00 (5.00)</td>
</tr>
<tr>
<td>Premorbid adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>1.91 (1.4)</td>
<td>1.8 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>2.48 (1.3)</td>
<td>2.3 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUP in weeks&lt;sup&gt;d&lt;/sup&gt;</td>
<td>168 (225)</td>
<td>68.0 (1072)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS 5 factors&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11.6 (4.73)</td>
<td>11.0 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16.3 (6.21)</td>
<td>16.0 (24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory</td>
<td>5.03 (1.56)</td>
<td>4.00 (6.00)</td>
<td></td>
<td></td>
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<tr>
<td>Disorganized</td>
<td>8.47 (2.81)</td>
<td>8.00 (15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>8.71 (3.40)</td>
<td>8.00 (14.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: AoM, awareness of the mind of the other

<sup>a</sup> Mann-Whitney test.

<sup>b</sup> The highest parental vocational education for either parent.

<sup>c</sup> Including CTQ subcategories with moderate-severe cut-off scores, institutionalization and separation from primary caregivers.

<sup>d</sup> Three missing due to schizophrenia simplex diagnosis.

<sup>e</sup> Van der Gaag's 5 factor model (van der Gaag 2006).
Figure 1. The distribution of positive and negative symptoms in symptom groups (N=94)

Notes: Cluster groups based on positive and negative symptom z-scores
<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
<th>9.</th>
<th>10.</th>
<th>11.</th>
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<tbody>
<tr>
<td>1. MAS sum score</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. DUP</td>
<td>-.015</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Number of adversities</td>
<td>.139</td>
<td>.240</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. PAS academic</td>
<td>-.138</td>
<td>-.014</td>
<td>.000</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>5. PAS social mean</td>
<td>.092</td>
<td>.176</td>
<td>-.060</td>
<td>.200</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>6. Positive symptoms†</td>
<td>-.113</td>
<td>.352</td>
<td>-.120</td>
<td>.126</td>
<td>.228</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>7. Negative symptoms†</td>
<td>-.417</td>
<td>-.176</td>
<td>-.065</td>
<td>-.014</td>
<td>.050</td>
<td>-.047</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>8. Self-reflectivity</td>
<td>.902</td>
<td>-.031</td>
<td>.145</td>
<td>-.95</td>
<td>.124</td>
<td>-.094</td>
<td>-.415</td>
<td>1</td>
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<tr>
<td>9. AoM</td>
<td>.757</td>
<td>.033</td>
<td>.130</td>
<td>-.220</td>
<td>-.069</td>
<td>-.065</td>
<td>-.327</td>
<td>.564</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>10. Decentration</td>
<td>.776</td>
<td>.111</td>
<td>.162</td>
<td>-.210</td>
<td>.063</td>
<td>-.025</td>
<td>-.355</td>
<td>.660</td>
<td>.701</td>
<td>1</td>
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<tr>
<td>11. Mastery</td>
<td>.828</td>
<td>-.074</td>
<td>.056</td>
<td>-.028</td>
<td>.122</td>
<td>-.140</td>
<td>-.286</td>
<td>.650</td>
<td>.424</td>
<td>.444</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: AoM, awareness of the mind of the other
* p < 0.05, ** p < 0.01
† Positive and negative symptoms as defined by van der Gaag (van der Gaag et al., 2006)
Table 3. Comparison of baseline characteristics between groups based on positive and negative symptoms (N = 83)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>F(15, 231)</th>
<th>( \eta^2 )</th>
<th>Post hoc Comparisons</th>
</tr>
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<tbody>
<tr>
<td><strong>Standardized</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>discriminant</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>function</strong></td>
<td>Low negative/low positive (n=34)</td>
<td>Low negative/high positive (n=14)</td>
<td>High negative/low positive (n=12)</td>
<td>High negative/high positive (n=23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>coefficients</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS-A total</td>
<td>0.96</td>
<td>16.03 (3.19)</td>
<td>14.57 (3.33)</td>
<td>11.71 (3.80)</td>
<td>13.35 (2.99)</td>
<td>6.40</td>
<td>&lt; 0.001 1 &gt; 3, 4; 2 &gt; 3</td>
</tr>
<tr>
<td>DUP ( ^{b} )</td>
<td>0.54</td>
<td>119.09 (177.06)</td>
<td>179.21 (214.17)</td>
<td>129.92 (248.68)</td>
<td>192.26 (225.54)</td>
<td>2.57</td>
<td>0.06 0.09 3 &lt; 2, 4</td>
</tr>
<tr>
<td>Number of adversities ( ^{c} )</td>
<td>-0.40</td>
<td>2.88 (1.97)</td>
<td>2.50 (1.61)</td>
<td>2.92 (1.98)</td>
<td>3.04 (1.97)</td>
<td>0.24</td>
<td>0.87 0.01</td>
</tr>
<tr>
<td>Premorbid academic</td>
<td>0.31</td>
<td>2.36 (1.15)</td>
<td>1.61 (1.37)</td>
<td>2.25 (0.98)</td>
<td>2.93 (1.53)</td>
<td>1.38</td>
<td>0.26 0.05</td>
</tr>
<tr>
<td>Premorbid social ( ^{b} )</td>
<td>-0.44</td>
<td>1.90 (1.28)</td>
<td>2.83 (1.23)</td>
<td>1.78 (1.62)</td>
<td>2.38 (1.45)</td>
<td>1.15</td>
<td>0.35 0.04</td>
</tr>
</tbody>
</table>

\( ^{a} \) MANOVA comparing metacognitive total score (MAS-A), DUP, number of adversities, premorbid academic and social functioning. Pillais’ Trace \( \approx 0.42 \), \( F(15, 231) = 2.51, \quad \eta^2 = 0.14 \).

\( ^{b} \) DUP and premorbid social adjustment were entered as logarithmically transformed variables.

\( ^{c} \) Including CTQ subcategories with moderate-severe cut-off scores, institutionalization and separation from primary caregivers.

Table 4. Comparisons of metacognitive subscales between symptom groups (N = 94)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>( \chi^2 ) (3)</th>
<th>( p = )</th>
<th>( U^{b} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low positive/low negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( (n=39) )</td>
<td>Mean (SD)</td>
<td>Mean rank</td>
<td>Mean (SD)</td>
<td>Mean rank</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reflectivity</td>
<td>6.00 (1.45)</td>
<td>60.19</td>
<td>5.20 (1.31)</td>
<td>46.80</td>
<td>4.50 (1.28)</td>
<td>33.31</td>
<td>16.73</td>
</tr>
<tr>
<td>AoM</td>
<td>3.68 (1.14)</td>
<td>53.21</td>
<td>3.53 (0.83)</td>
<td>53.17</td>
<td>3.06 (0.81)</td>
<td>37.06</td>
<td>3.21 (0.66)</td>
</tr>
<tr>
<td>Decentration</td>
<td>1.44 (0.65)</td>
<td>56.97</td>
<td>1.20 (0.53)</td>
<td>48.03</td>
<td>0.88 (0.59)</td>
<td>34.00</td>
<td>1.04 (0.51)</td>
</tr>
<tr>
<td>Mastery</td>
<td>5.47 (1.15)</td>
<td>60.99</td>
<td>4.30 (1.78)</td>
<td>42.60</td>
<td>3.88 (1.75)</td>
<td>35.00</td>
<td>4.40 (1.08)</td>
</tr>
</tbody>
</table>

\( ^{a} \) Kruskal-Wallis analysis of variance and post hoc Mann-Whitney. AoM, awareness of the mind of the other

\( ^{b} \) A total of 94 persons with FEP was divided into groups based on positive and negative symptoms.

\( ^{c} \) Bonferroni correction applied for six tests per subscale, \( p = 0.008 \).