Synergistic effects of childhood adversity and polygenic risk in first episode psychosis: The EU-GEI study

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ABSTRACT

A history of childhood adversity is associated with psychotic disorder, with an increase in risk according to the number of exposures. However, it is not known why only some exposed individuals go on to develop psychosis. One possibility is pre-existing polygenic vulnerability. Here we investigated, in the largest sample of first-episode psychosis (FEP) cases to date, whether childhood adversity and high polygenic risk score combine synergistically to increase the risk of psychosis, over and above the effect of each alone.

Method: We assigned a schizophrenia-polygenic risk score (SZ-PRS), calculated from the Psychiatric Genomics Consortium (PGC2), to all participants in a sample of 397 FEP patients and 702 controls from the incidence and case-control component of EU-GEI study. Only participants of European ancestry were included in the study. A history of childhood adversity was collected using the Childhood Trauma Questionnaire (CTQ). Synergistic effects using the interaction contrast ratio (ICR) were estimated as: trauma and PRS–trauma–PRS+1, with adjustment for potential confounders.

Results: There was some evidence that the combined effect of childhood adversities and polygenic risk was greater than the sum of each alone, as indicated by an ICR greater than 1 (i.e., ICR 1.30, 95% CI: -1.27-3.87). Dividing into subtypes of childhood adversities, the strongest synergetic effect was observed for physical abuse (ICR 7.76, 95% CI: -6.24-21.77).

Conclusions: Our findings suggest possible synergistic effects of genetic liability and childhood adversity experiences in the onset of first-episode psychosis, but larger samples are needed to increase precision of estimates.

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INTRODUCTION

Psychotic disorders such as schizophrenia have detrimental societal, economical and individual costs (Charlson *et al.*, 2018). A history of childhood adversity is one of the strongest environmental predictors of mental illness, crossing boundaries of affective and psychotic illnesses (van *et al.*, 2013). A history of adversity is associated with up to 3-fold increased risk of psychotic disorder with an increase in risk according to number and severity of exposures (Aas *et al.*, 2016, Varese *et al.*, 2012). However, it is not known why only some exposed individuals go on to develop psychosis. A plausible explanation concerns that exposed individuals differ in their pre-existing biological vulnerability to psychosis, given that these disorders are characterised by several variants with ~~a~~ small effect sizes (Schizophrenia Working Group of the Psychiatric Genomics C, 2014, Tesli *et al.*, 2014, Zheutlin *et al.*, 2019). However, it is yet to be determined if both high polygenic risk and childhood trauma increase the risk above that of each alone (additive synergistic effects).

Initial studies investigating interactions between exposure to childhood adversities and underlying genetic susceptibility in schizophrenia focused mainly on candidate genes, including AKT1, COMT, BDNF; findings have been inconclusive (Aas *et al.*, 2014, Modinos *et al.*, 2013, Trotta *et al.*, 2019). Studying single candidate genes may miss important aspects of the etiology of psychoses, as psychotic disorders are polygenic in nature (Vassos *et al.*, 2017).

Emerging as a consequence of this limitation, studies using polygenic risk score (PRS) have emerged. PRS are calculated by using subsets of single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS), that are selected according to their p-value and weighted by their effect size, to calculate a PRS for each individual in an independent validation sample. The PRS can then be tested for its ability to differentiate between cases

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and controls in the validation dataset (Dudbridge, 2013, Purcell *et al.*, 2009). The current PRS explains around 7% of the variation in the liability for schizophrenia assuming a lifetime risk of 1% (Schizophrenia working group, 2014). The development of the PRS has opened a new avenue for studying the underlying genetic susceptibility as a whole, while excluding biases related to the selection of specific candidate genes and/or genetic variants. Such a PRS can, in turn, be used to study interaction effects with environmental risk factors.

In major depressive disorder (MDD), findings of interactions between polygenic risk for MDD and childhood adverse events have been mixed (Mullins *et al.*, 2016, Peyrot *et al.*, 2014, Peyrot *et al.*, 2017), with the most recent and largest study rejecting interaction effects (Peyrot *et al.*, 2017). In chronic SZ, a recent study provided some evidence of synergistic effects, that is the effect arising when polygenic risk and childhood trauma were added into the same model, was greater than the sum of their individual effects (Guloksuz *et al.*, 2019). In first-episode psychosis, only one pilot study (N< 200) has to date investigated interaction between childhood trauma and SZ-PRS (Trotta *et al.*, 2016), concluding that higher SZ-PRS and childhood adversities each predicted case status independent of each other with no strong evidence of interactions, however synergistic effects using the interaction contrast ratio (ICR) were not investigated. Therefore, the current study aimed to investigate synergistic effects of SZ polygenic risk scores and childhood adversities in first-episode psychosis status in a large (N>1000) multi-centre study (EU-GEI). Our study is the first study to investigate synergistic effects applying the interaction contrast ratio (ICR) of polygenic risk and childhood adversity on the risk of developing a first-episode psychosis diagnosis. Additive interaction will be applied as additive interactions has been suggested to correspond to mechanistic interaction and specifically useful to test biological interactions (VanderWeele and Knol, 2014).

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Commented [MA6R5]: Thanks Antonella. I have clarified that the ICR was not reported in the previous paper, thus this is the first time ICR have been investigated.

Commented [LA7]: Would it worth mentioning couple of papers exploring the genetic liability with twin designs? Maybe in the discussion.
This one just came out: Evidence that the association of childhood trauma with psychosis and related psychopathology is not explained by gene-environment correlation: A monozygotic twin differences approach

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Our hypothesis was that the combined effect on odds of psychosis of the two (polygenic risk and a history of childhood adverse events) would be greater than the sum of their individual effects.

METHODS

Study design and participants

The sample was drawn from the larger EU-GEI (European Network of National Schizophrenia Networks Studying Gene-Environment Interactions) multi-centre study. The EUGEI study is a multi-centre incidence and case-sibling-control study of genetic and environmental determinants of psychotic disorders (Di Forti *et al.*, 2019, Quattrone *et al.*, 2019). For the analyses presented in this paper, only participants with a European ancestry and who had data on polygenic risk score of schizophrenia and childhood adverse events were included. Patients and controls were recruited from 16 different sites as part of the EU-GEI study (for recruitment an overview, see Supplementary Material Table S1).

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Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L, Selten JP, Szöke A, Llorca PM, Tortelli A, Arango C. The EUropean Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EU-GEI): Incidence and First-Episode Case–Control Programme. Social Psychiatry and Psychiatric Epidemiology. 2020 Jan 23:1-3.

Commented [CGA10]: In the full study, this was 17 sites.

To be included in the study, all patients had to be within their first-episode of psychosis. The diagnosis was confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness within in the EU-GEI consortia (McGuffin *et al.*, 1991, Quattrone *et al.*, 2019). Patients were identified by clinical trained researchers who carried out regular checks across the 16 catchment area Mental Health Services. Exclusion criteria included previous treatment for psychosis, and a diagnosis of organic psychosis (ICD-10: F09) or transient psychotic symptoms resulting from acute intoxication (ICD- 10: F1X.5).

Controls with no lifetime psychotic disorder were recruited from the same population as the cases using guided Random and Quota sampling strategies. Exclusion criteria for both controls and cases, and an

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intelligence quotient <70. Written informed consent was obtained from those who agreed to participate in the case-control study.

Sociodemographic

Information on demographics, premorbid characteristics, and social circumstances were collected from cases and controls using the Medical Research Council (MRC) Socio-demographic Schedule modified version (Mallett *et al.*, 2002).

Childhood Trauma Questionnaire (CTQ)

To measure adverse childhood events, we used the Childhood Trauma Questionnaire (CTQ), a retrospective questionnaire enquiring about potentially traumatic experiences in childhood with answers ranging from "never true", through "rarely true", "sometimes true", "often true", to "very true", yielding a total score, as well as five sub-scores: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. The reliability and validity of the CTQ have been demonstrated previously. Data were dichotomized for each childhood adversity domain (0="absent" and 1="present"), based on the moderate to severe cut-off score from the CTQ Manual (Bernstein *et al.*, 1994) using the following cut-off score for each domain: $\geq$ 13 for emotional abuse; $\geq$ 10 for physical abuse; $\geq$ 8 for sexual abuse; $\geq$ 15 for emotional neglect; and $\geq$ 10 for physical neglect. Sensitivity analysis was conducted analysing CTQ as a continuous measure following the procedures from the CTQ Manual with scores ranging from 25-125 (Bernstein *et al.*, 1994).

Genotyping and polygenic risk calculations

Samples were genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK) using a custom Illumina HumanCoreExome-24 BeadChip genotyping array

covering 570,038 genetic variants. To identify ethnic groups, we combined our dataset with the 1000 Genome Project (1000G), phase 3 and performed Principal Component PC Analysis on the overlapping SNPs. Only Europeans were included in this study. Individuals of European ancestry were defined as having PC values within 6 standard deviations from the mean PC of the EUR in 1000G, and retained for the downstream analyses. Polygenic risk scores (PRS) for schizophrenia (SZ-PRS) were generated using PRSice from the summary results of the PGC analysis of schizophrenia, wave 2 (Schizophrenia Working Group of the Psychiatric Genomics C, 2014). Clumping was performed to obtain SNPs in approximate linkage disequilibrium with an $r^2 < 0.25$ within a 250kb window. PRS were calculated within Europeans only and at P-value thresholds of 0.05 (Schizophrenia Working Group of the Psychiatric Genomics C, 2014). Further, each PRS was standardized to a mean of zero and standard deviation of 1, excluding the MHC region (Lewis and Vassos, 2017).

Statistics

The main analyses were carried out using the Statistical Package for Social Sciences, Version 25.0 (SPSS Inc.). Logistic regression was used to estimate the odds of psychosis for childhood adverse events and SZ-PRS. The cumulative effect of childhood adversity (zero, one or two or more types of trauma) was categorised using moderate to severe cut off score from the CTQ Manual (Bernstein *et al.,* 1994) as previously mentioned. Sensitivity analyses were conducted analyzing childhood adversity as continuous variables.

The association between the schizophrenia PRS (SZ-PRS) and the presence or absence of (i) psychotic disorder and (ii) childhood adversity (i.e., gene–environment correlation) was tested using a linear regression model, controlling for population stratification (adjusting for ten principal component analysis, PCA), sex, age and education level, because such factors could potentially bias the results (see Trotta *et al.,* 2016).

Additive models to test interaction as departure from additivity were applied using the Interaction Contrast Ratios (ICR) (Knol *et al.*, 2007, Knol and VanderWeele, 2012). This means that the combined effect of SZ-PRS and childhood adverse events is greater than the sum of their individual effects. The ICR was estimated as $OR_{\text{exposure and PRS}^-} - OR_{\text{exposure}^-} - OR_{\text{PRS}^+} + 1$. ICR greater than zero indicates a positive deviation from additivity. For the ICR, SZ-PRS was dichotomized into two groups (below or 75th percentile and above) using the same method as described in Guloksuz *et al.* (2019), and data on childhood adversity was analyzed using the predefined $<$ or $\geq$ moderate to severe cut off scores described in the CTQ Manual (Bernstein *et al.*, 1994) (see respective section). The confidence intervals for the ICRs for each model were calculated using the delta method (Hosmer, 1992). To test the joint effects of environmental exposures and genetic score, we entered the four states occasioned by the combination of each exposure and binary SZ-PRS risk state as independent variables (three dummy variables), and case status as the dependent variable, in multilevel logistic regression models. Analyses were adjusted for site, sex, age, and ten principal components (covariates added into the logistic regression model). Sensitivity analyses were conducted examining PRS x childhood adversity additive interaction model analyzing PRS as a continuous variable using a residual score of the PRS regressing out the effect of site, age, sex and ten principal components following the principles described by (VanderWeele and Knol, 2014).

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RESULTS

Sample characteristics are shown in Table 1. Compared with controls, cases had a lower level of education (p<0.001). Patients were also more likely to be men and were younger than the control group (p<0.001, see Table 1).

-Please insert Table 1 here-

Childhood adversity and polygenic risk in first-episode psychosis

Cases reported more childhood adversities than controls (see Table 2). Patients were four times more likely to report two or more childhood adversities than controls and the OR was higher for multiple (Odds ratio, OR: 4.59; 95% CI: 3.17-6.65; p<0.001) than single adverse childhood experiences (Odds ratio, OR: 2.07; 95% CI: 1.48-2.89; p<0.001, see Table 2). Emotional neglect was the most prevalent form of adversity in both cases (N=95 [24%]) and in controls (N=77 [11%]). Sensitivity analysis of childhood adverse events as a continuous variable confirmed higher prevalence of trauma in the cases compared with controls (see Supplementary Material, Table S2).

-Please insert Table 2 here-

A higher polygenic score (PRS) was associated with psychosis case status (Odds ratio, OR: 1.76; 95% CI: 1.51-206; p<0.001), and the association held when the sample was restricted to cases with an ICD-10 diagnosis of Schizophrenia Spectrum disorders (Odds ratio, OR: 1.92; 95% CI: 1.57-2.35; p<0.001). Data were adjusted for age, sex, site and genetic variation within the European sample using principal component analyses (PCA).

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Also you might want toad it as covariate for the rest of the analysis if there is a significant difference in SES between cases and controls

Commented [MA15R14]: Thanks for this. We have adjusted for education levels in the analysis comparing patients to controls on childhood trauma and found that patients report more trauma than controls also after adjusting for education (as a proxy for SES).

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Gene-environment correlation

To test the possibility of gene-environment correlation, we examined the associations between SZ-PRS and childhood adversity, adjusting for PCs, sex, and age. When the childhood adversities were analysed as a binary variable, no association was observed between SZ-PRS and childhood adversities is either cases or controls (OR: 0.03; 95% CI: -0.14-0.24; p=0.60, Odds ratio, OR: 0.03; 95% CI: -0.10-0.24; p=0.43, respectively, see Table 3). Sensitivity analysis testing childhood adversities as a continuous score suggested a small but positive association with SZ-PRS in the controls, but not in cases (ß=0.09; 95% CI: 0.02-0.19, p=0.02, ß=0.02; 95% CI:-0.06-0.09, p=0.67, respectively, see Supplementary material Table S3).

-Please insert Table 3 here-

Synergistic effects of childhood adversity and polygenic risk in first-episode psychosis

The combined effect of childhood adversity (at least one type of trauma reaching moderate to severe levels) and polygenic risk was greater than the sum of each alone, but the CI included zero ICR of 1.30 (95% CI:-1.27-3.87, see Table 4, Figure 1). Explorative analyses dividing into subtypes of childhood adversity, showed the largest ICR for physical abuse (ICR=7.76, 95% CI: -6.24-21.77) and physical neglect (ICR=3.13, 95% CI: -2.00-8.27), see Table 5, Figure 2a-b). The interaction contrast ratio (ICR) was above zero for physical abuse, emotional abuse, emotional neglect and physical neglect, but confidence interval included zero for all analyses. Data were adjusted for site, sex, age and ten principal components.

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-Please insert Table 4, Table 5 and Figure 1, 2a, 2b here-

Sensitivity analyses confirmed similar findings analyzing SZ-PRS as a continuous variable. Still the combined effect of childhood adversities (at least one type of trauma reaching moderate to severe levels) and polygenic risk was greater than the sum of each alone (ICR=1.25, 95%; CI:-15.03-67.81).

DISCUSSION

Our findings suggest a modest combined effect of genetic liability and childhood adverse events in the onset of first-episode psychosis (FEP). Our study is, to the best of our knowledge, the first to present synergistic effects of polygenic risk and childhood adverse events in FEP. The combined effect of childhood adversities (at least one type of trauma reaching moderate to severe levels) and genetic liability for schizophrenia was greater than the sum of each alone, but the sample was underpowered and confidence intervals were wide, thus larger studies are needed before we can conclude with certainty. Dividing into subtypes of childhood adverse events, explorative analyses revealed an interaction contrast ratio (ICR) above zero for physical abuse, emotional abuse, emotional neglect and physical neglect, with the largest ICR for physical abuse (7.76), and physical neglect (3.13). Synergistic effect of polygenic risk for schizophrenia (SZ-PRS) and childhood adverse events was recently reported in chronic schizophrenia (Guloksuz *et al.*, 2019), and our findings are compatible with a similar effect in patients with a first-episode psychosis.

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In line with previous findings the polygenic risk score for schizophrenia (SZ-PRS) predicted psychotic disorder in this large multi-centre study. In addition, the cumulative effect of childhood adversity was associated with case/control status, consistent with previous studies of childhood adverse events and increased risk for psychosis (Church *et al.*, 2017, Shevlin *et*

al., 2008, Trotta *et al.*, 2016), with higher odds ratio (OR) in participants with multiple versus one type of trauma. Similar to the study by Trotta *et al.*, (2016), we found no correlation between genetic liability for schizophrenia and childhood adversity assessed as a binary measure. However, sensitivity analyses suggested a small positive correlation between polygenic risk for schizophrenia and childhood adverse events in the unaffected controls, but not in the cases. Given that parental psychopathology may increase the likelihood of a child being maltreated (Sidebotham *et al.*, 2001), it could be that "the genetic substrate of the parents leads to both the abuse and to the illness in the children" (Torrey, 2002), thus, in favor of a positive correlation. However, a complex interplay between a variety of factors are probably present, including, but not limited to factors that are not within the direct control of the individual (e.g., socioeconomic status). Our results are therefore partially consistent with these finding showing a correlation in the unaffected controls, but not in the cases. It could also be speculated that we had greater statistical power in the larger healthy control sample (N=702), than the smaller patients' sample (N=397) which could be reflected in the findings above. However, the high levels of childhood adversity in cases were not a consequence of genetic vulnerability in our sample.

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As described by Trotta et al., (2016) childhood maltreatment may trigger maladaptive believes about the self and the world, including a negativity bias in attribution of others' intentions, disruption of the self and low personal control of events which may all trigger and maintain psychotic symptoms (Garety *et al.*, 2007, Howes and Murray, 2014, Rajkumar, 2014). As suggested in the stress-diatheses model (Pruessner *et al.*, 2017, Walker and Diforio, 1997) exposure to childhood adversity may "sensitize" an individual with a genetic risk for psychosis to later life stressors with exaggerated emotional responses and

subsequent psychotic symptoms. This is supported by a recent study showing elevated hair cortisol (measure of stress over time) in psychotic adults patients with childhood adverse events experiences (Aas *et al.*, 2019b), indicating long-term changes of the HPA axis following childhood adverse events. It has also been suggested that childhood adverse events and stress lead to an imbalance of the dopamine neurotransmission between prefrontal cortex and mesolimbic circuits (Deutch *et al.*, 1990), which is relevant to positive symptom formation (Kapur *et al.*, 2005) and long-term changes in the HPA system following trauma events (Aas *et al.*, 2019b). Our findings, in the largest study to date, suggest modestly synergistic effects of genetic liability and childhood adversity experiences in the onset of first-episode psychosis. However, these findings should be interpreted with caution as the confidence intervals of the interaction contrast ratios were large and included zero. It should also be noted that recent studies indicate independent risk of childhood adverse events and genetic risk in severe mental disorders (Aas *et al.*, 2019a, Lecei *et al.*, 2019), and due to the large variation of estimates within our study we cannot rule out the possibility of no effect.

Limitations Childhood trauma was reported retrospectively, with the inherent weakness of the retrospective design. A recent meta-analysis study suggests low overlap between retrospective and prospective collection of childhood trauma (Baldwin *et al.*, 2019). However, this study reported large heterogeneity within the meta-analysis. Albeit, it should be mentioned that reliance solely on retrospective assessment methods may have led to a proportion of non-exposed group being misclassified and thus affecting the results (Newbury *et al.*, 2018, Reuben *et al.*, 2016), thus, these results should be interpreted with caution until replicated in independent studies. As previously mentioned, the ICR had large confidence intervals and included zero, thus the ICR should be interpreted with caution. As discussed by Knol and VanderWeele 2012 (Knol and VanderWeele, 2012), even though CIs include zero,

if the additive estimate (here ICR) is above zero and CIs show a trend towards a positive interaction (skewed above zero), there is a strong indicator that the estimated effect on the additive scale is above zero and synergistic effects are present.

To sum up, our study suggests that both a history of childhood adverse events and polygenic risk for schizophrenia modestly increase the risk for a psychotic illness, above that of childhood adverse events or polygenic risk alone. Thus, our findings indicate that experiencing childhood adverse events in individuals with high genetic risk for schizophrenia increases the likelihood of developing a psychotic illness more than individuals with low genetic risk for schizophrenia, however the large confidence intervals indicate that the findings should be interpreted with caution before replicated in larger independent samples.

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Commented [AM21]: Additional funding to be added

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CONFLICT OF INTEREST

No conflicts of interest.

CONTRIBUTORS

Monica Aas, Luis Alameda, Marta di Forti, Diego Quattrone, Robin Murray and Craig Morgan wrote the first draft. All authors read and approved the final Manuscript.

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