



The relationship between genetic liability, childhood maltreatment, and IQ: findings from the EU-GEI multicentric case–control study

Lucia Sideli, Monica Aas, Diego Quattrone, Daniele La Barbera, Caterina La Cascia, Laura Ferraro, Luis Alameda, Eva Velthorst, Giulia Trotta, Giada Tripoli, et al.

► To cite this version:

Lucia Sideli, Monica Aas, Diego Quattrone, Daniele La Barbera, Caterina La Cascia, et al.. The relationship between genetic liability, childhood maltreatment, and IQ: findings from the EU-GEI multicentric case–control study. *Social Psychiatry and Psychiatric Epidemiology*, 2023, 58 (10), pp.1573 - 1580. 10.1007/s00127-023-02513-0 . inserm-04197570

HAL Id: inserm-04197570

<https://inserm.hal.science/inserm-04197570>

Submitted on 6 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



The relationship between genetic liability, childhood maltreatment, and IQ: findings from the EU-GEI multicentric case–control study

Lucia Sideli^{1,2,3} · Monica Aas^{2,4,5,6} · Diego Quattrone⁴ · Daniele La Barbera³ · Caterina La Cascia³ · Laura Ferraro³ · Luis Alameda^{2,7,8,9} · Eva Velthorst¹⁰ · Giulia Trotta² · Giada Tripoli^{2,3,11} · Adriano Schimmenti¹² · Andrea Fontana¹ · Charlotte Gayer-Anderson^{13,14} · Simona Stilo^{2,15} · Fabio Seminerio³ · Crocettarachele Sartorio³ · Giovanna Marrazzo³ · Antonio Lasalvia¹⁶ · Sarah Tosato¹⁶ · Iaria Tarricone¹⁷ · Domenico Berardi¹⁸ · Giuseppe D'Andrea¹⁸ · EU-GEI WP2 Group · Celso Arango¹⁹ · Manuel Arrojo²⁰ · Miguel Bernardo^{21,22} · Julio Bobes²³ · Julio Sanjuán²⁴ · Jose Luis Santos²⁵ · Paulo Rossi Menezes²⁶ · Cristina Marta Del-Ben²⁷ · Hannah E. Jongsma^{28,29} · Peter B. Jones^{30,31} · James B. Kirkbride²⁸ · Pierre-Michel Llorca³¹ · Andrea Tortelli³² · Baptiste Pignon^{33,34,35} · Lieuwe de Haan³⁶ · Jean-Paul Selten^{37,38} · Jim Van Os^{2,38,39} · Bart P. Rutten³⁸ · Richard Bentall⁴⁰ · Marta Di Forti⁴ · Robin M. Murray² · Craig Morgan^{13,14} · Helen L. Fisher^{4,14}

Received: 24 January 2023 / Accepted: 4 June 2023 / Published online: 19 June 2023
© The Author(s) 2023

Abstract

This study investigated if the association between childhood maltreatment and cognition among psychosis patients and community controls was partially accounted for by genetic liability for psychosis. Patients with first-episode psychosis ($N=755$) and unaffected controls ($N=1219$) from the EU-GEI study were assessed for childhood maltreatment, intelligence quotient (IQ), family history of psychosis (FH), and polygenic risk score for schizophrenia (SZ-PRS). Controlling for FH and SZ-PRS did not attenuate the association between childhood maltreatment and IQ in cases or controls. Findings suggest that these expressions of genetic liability cannot account for the lower levels of cognition found among adults maltreated in childhood.

Keywords Childhood adversity · Cognition · Family history of psychosis · First episode · Polygenic risk score · Psychosis

Introduction

Literature suggests that the association between childhood maltreatment (i.e., abuse and neglect) and later cognitive functioning might be weaker among people with psychosis compared with unaffected controls [1]. Indeed, in a previous study on the EU-GEI sample of patients with first-episode psychosis (FEP) and community controls, we found that the association between reported exposure to maltreatment in childhood and a lower Intelligence Quotient (IQ) in adulthood was weaker among patients than controls [2]. This difference might be due to the confounding effect of other risk factors associated with both childhood maltreatment and cognition that are more prevalent among people with psychosis than unaffected controls, such as genetic liability

to psychotic disorders [3–7]. Moreover, among individuals with psychosis, the impact of environmental risk factors (such as maltreatment) on cognition might be reduced by a floor effect related to genetic liability and neurodevelopmental alterations [8, 9].

Only a few studies have explored the relationship between genetic liability, childhood maltreatment, and cognition among people experiencing psychosis. For instance, the NAPLS-3 study found that among youth at clinically high risk for psychosis, family history of psychosis (FH) was associated with both greater trauma exposure and lower IQ compared with no-FH [10]. Polygenic risk scores for schizophrenia (SZ-PRS) [11, 12] have been associated with lower IQ in the general population [9, 13–15], but the findings have not consistently been replicated among people with schizophrenia [16–18]. Although SZ-PRS has also shown a modest association with childhood maltreatment [19], to our knowledge no study has investigated the role of genetic liability for psychosis in the association between childhood maltreatment and cognition.

Craig Morgan and Helen L. Fisher have contributed equally to this work and they are joint senior authors.

Extended author information available on the last page of the article

Therefore, in this study, we aimed to investigate whether the association between childhood maltreatment (overall maltreatment, and abuse and neglect separately) and IQ could be partially accounted for by genetic liability (defined as either having FH or based on SZ-PRS). We hypothesised that genetic liability to psychosis would contribute to attenuating the association between reported exposure to maltreatment in childhood and lower IQ in adulthood among FEP patients but not among controls.

Methods

Participants and procedure

The EU-GEI study is a multi-centre case–control study carried out between May 2010 and April 2015 in five European countries and Brazil [20, 21]. The study was approved by the Internal Review Boards of the study centres and conducted according to International ethical standards.

People with FEP were individuals aged 18–64, living in the study catchment areas, who approached mental health services for the first time for a primary diagnosis of a psychotic disorder (ICD-10 diagnoses: F20–F33) during the study period. Community controls were individuals who were representative of the same population as the cases, and who had never been referred or treated for psychotic disorders. Information about inclusion and exclusion criteria, sampling methods, and diagnostic procedures, have been detailed elsewhere [21, 22] and are described in the Supplementary Materials.

Measures

Cognitive functioning was estimated from IQ, assessed using an abbreviated, psychometrically robust version of the Wechsler Adult Intelligence Scales (WAIS-III) [23–25].

Genetic liability was defined as: (a) family history of psychosis (FH) and (b) polygenic risk scores for schizophrenia (SZ-PRS). FH was defined as having a first-degree relative affected by a psychotic disorder and assessed using the Family Interview for Genetic Studies (FIGS) [26]. SZ-PRSs were calculated only on the sub-sample of European ancestry participants, using the genotype procedure, population stratification, and SZ-PRS calculation as described previously [27–29] and in the Supplementary Materials.

Self-reported exposure to childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ) [30]. Mean ratings for physical, sexual, and emotional abuse items were used to create a childhood abuse score, mean ratings for physical and emotional neglect items were used to create a childhood neglect score, and the mean of all items was used to create an overall childhood maltreatment score.

Consistent with previous studies [2, 8], these variables were dichotomised using the 80th percentile of the control group's score as the cut-off value. These cut-offs were identical to those used in the original study [2]. In the subset with SZ-PRS data, the empirically derived cut-off used to calculate dichotomic measures of childhood abuse (present/absent) was slightly lower than that used in the original study (1.33 vs. 1.40, respectively).

Analyses

General linear regression models stratified for cases and controls were conducted to explore whether the association between overall childhood maltreatment (and separately childhood abuse and childhood neglect) and IQ (model 1), was attenuated by the inclusion in the model of FH or SZ-PRS (model 2). The analyses were then additionally controlled for sex, age, ethnicity, education, study country, and lifetime cannabis use (model 3); and then also for current use of antipsychotics (model 4) only in the FEP group. Measurement of covariates is described in the Supplementary Materials. Results are reported as regression coefficients (B) and standardized regression coefficients (β). Analyses were run using the Statistical Package for the Social Sciences (SPSS) program version 27.0.

Results

Association between childhood maltreatment, FH, and IQ

Information about FH was available for 91.1% of the FEP cases ($n = 755$) and 95% of controls ($n = 1219$) from the original sample (see Supplementary Table 1 for sample demographics). Associations between case status and (i) childhood maltreatment and (ii) lower IQ are reported in Supplementary Table 2 and were similar to those detected in the full sample [2].

In the crude models, IQs were on average substantially lower among community controls exposed to childhood maltreatment ($B = -5.29 [-7.86, -2.72]$, $p < 0.001$), childhood abuse ($B = -6.27 [-8.89, -3.65]$, $p < 0.001$), and childhood neglect ($B = -5.16 [-7.69, -2.63]$, $p < 0.001$), compared with unexposed controls. Among people with FEP, only childhood neglect was associated with lower IQ ($B = -2.90 [-5.50, -0.29]$, $p = 0.029$) (see Table 1 & Supplementary Table 3)—and to a more modest extent than among controls.

FH was more prevalent among FEP cases than among controls (OR = 3.10 [2.23, 4.31], $p < 0.001$). FH was associated with childhood abuse in the control group (OR = 1.94 [1.09, 3.47], $p = 0.025$) and with childhood neglect in both groups (controls: OR = 1.88 [1.06, 3.32], $p = 0.030$; FEP:

Table 1 Association between childhood maltreatment and IQ controlled for family history of psychosis and social and clinical confounders

Unstandardized models	Model 1			Model 2			Model 3			Model 4		
	<i>B</i>	95% CI	<i>p</i>	<i>B^a</i>	95% CI	<i>p</i>	<i>B^{a+b}</i>	95% CI	<i>p</i>	<i>B^{a+b+c}</i>	95% CI	<i>p</i>
Controls	<i>N</i> =1219			<i>N</i> =1219			<i>N</i> =1216			<i>N</i> =705		
Overall maltreatment*	-5.29	-7.86, -2.72	<0.001	-5.25	-7.82, -2.68	<0.001	-2.30	-4.55, -0.54	0.045			
Abuse	-6.27	-8.89, -3.65	<0.001	-6.22	-8.85, -3.60	<0.001	-3.08	-5.36, -0.79	0.008			
Neglect	-5.16	-7.69, -2.63	<0.001	-5.11	-7.65, -2.57	<0.001	-2.67	-4.91, -0.44	0.019			
FEP patients	<i>N</i> =755			<i>N</i> =755			<i>N</i> =754					
Overall maltreatment*	-2.17	-4.78, -0.45	0.104	-2.09	-4.71, 0.53	0.118	-0.41	-2.75, 1.92	0.729	-0.07	-2.50, 2.35	0.954
Abuse	-0.42	-2.70, 2.61	0.975	0.01	-2.65, 2.66	0.996	1.57	-0.78, 3.92	0.191	2.25	-0.20, 4.70	0.071
Neglect	-2.90	-5.50, -0.29	0.029	-2.80	-5.42, -0.19	0.036	-0.96	-3.28, 1.38	0.422	-0.63	-3.06, 1.80	0.613
Standardized models	Model 1			Model 2			Model 3			Model 4		
	<i>Beta</i>	95% CI	<i>p</i>	<i>Beta^a</i>	95% CI	<i>p</i>	<i>Beta^{a+b}</i>	95% CI	<i>p</i>	<i>Beta^{a+b+c}</i>	95% CI	<i>p</i>
Controls	<i>N</i> =1219			<i>N</i> =1219			<i>N</i> =1216					
Overall maltreatment*	-0.30	-0.44, -0.15	<0.001	-0.30	-0.44, -0.15	<0.001	-0.13	-0.26, -0.00	0.045			
Abuse	-0.35	-0.50, -0.21	<0.001	-0.35	-0.50, -0.20	<0.001	-0.17	-0.30, -0.04	0.008			
Neglect	-0.29	-0.43, -0.15	<0.001	-0.29	-0.43, -0.15	<0.001	-0.15	-0.28, -0.03	0.019			
FEP patients	<i>N</i> =755			<i>N</i> =755			<i>N</i> =754					
Overall maltreatment*	-0.12	-0.26, 0.03	0.104	-0.12	-0.26, 0.03	0.118	-0.02	-0.15, 0.11	0.729	-0.00	-0.14, 0.13	0.954
Abuse	-0.00	-0.15, 0.15	0.975	-0.00	-0.15, 0.15	0.996	0.09	-0.04, 0.22	0.191	0.13	-0.01, 0.26	0.071
Neglect	-0.16	-0.30, -0.02	0.029	-0.16	-0.30, -0.01	0.036	-0.05	-0.18, 0.08	0.422	-0.04	-0.17, 0.10	0.613

CI confidence intervals, FEP first-episode psychosis, IQ intelligence quotient

^aAdjusted for family history of psychosis^bAdjusted for sex, age, ethnicity, education, study country, and lifetime cannabis use^cAdjusted for antipsychotic treatment*Exposure to overall childhood maltreatment, and separately childhood abuse, and childhood neglect were defined as mean CTQ > 80th percentile of the control group; significant associations ($p < 0.05$) are shown in bold type

OR = 1.54 [1.02, 2.33], $p = 0.039$). FH was not strongly associated with IQ in either group (controls: $B = -1.95$ [− 6.52, 2.62], $p = 0.403$; FEP: $B = -2.10$ [− 5.81, 1.62], $p = 0.269$) (see Supplementary Table 3). Multivariable analyses suggested that including FH in the model did not attenuate the association between childhood maltreatment and IQ in cases or in controls (see Table 1).

Association between childhood maltreatment, SZ-PRS, and IQ

Eight-hundred and fifty community controls and 488 FEP patients (i.e., 66.2% and 58.9% of the original sample, respectively) had complete measures of childhood maltreatment, IQ, and SZ-PRS (see Supplementary Table 4 for sample demographics).

In the control group, a 4–5-point decrease in IQ was associated with childhood maltreatment ($B = -5.11$ [− 8.12, − 2.10], $p < 0.001$), abuse ($B = -4.27$ [− 7.12, − 1.41], $p = 0.003$), and neglect ($B = -5.18$ [− 8.09, − 2.28], $p < 0.001$). In the FEP group, the association between childhood maltreatment ($B = -1.86$ [− 5.10, 1.39], $p = 0.261$), abuse ($B = -0.51$ [− 3.75, 2.73], $p = 0.757$), neglect ($B = -2.13$ [− 5.34; 1.09], $p = 0.194$), and IQ were of a similar size to those detected in the analyses of the full sample, although failed to reach significance.

SZ-PRS were higher in FEP cases than in controls ($B = 0.54$ [0.43, 0.65], $p < 0.001$). In the case group, SZ-PRS was modestly associated with childhood maltreatment (OR = 1.32 [1.03, 1.68], $p = 0.027$) and with childhood neglect (OR = 1.26 [0.99, 1.60], $p = 0.060$). However, in the control group, no associations were found (SZ-PRS and childhood maltreatment OR = 1.00 [0.78, 1.27], $p = 0.970$; abuse OR = 1.00 [0.79, 1.26], $p = 0.974$; neglect OR = 0.98 [0.77, 1.25], $p = 0.890$).

In the control group, higher SZ-PRS was marginally associated with lower IQ ($B = -1.42$ [− 2.93, 0.92], $p = 0.066$), as well as in the case group ($p = 0.180$). Multivariable analyses suggest that including SZ-PRS did not reduce the childhood maltreatment–IQ association in either the case or control group (see Supplementary Table 5).

Discussion

This study found that although FH and SZ-PRS were associated with a greater likelihood of reporting childhood maltreatment (indicating a potential gene–environment correlation), they were not so strongly associated with IQ, and did not attenuate the crude association between childhood maltreatment and IQ in either FEP cases or unaffected controls. These findings are consistent with previous studies suggesting that, although FH is three-to-seven times more

common among patients compared to controls [31, 32], its effect on psychosis risk seems relatively independent from the effect of childhood maltreatment, and vice versa [33, 34].

In the subset of European ancestry participants with complete information about childhood maltreatment, IQ, and SZ-PRS, there was evidence of an association between childhood maltreatment and poor cognition, which failed to reach statistical significance among FEP cases. This is different from our previous analysis of this dataset [2] and might be due either to insufficient power, or to the exclusion of non-European ancestry FEP patients (i.e., potentially the relationship between childhood maltreatment and IQ might be more evident among non-European ancestry FEP patients), or to both. Among both cases and controls, SZ-PRS was weakly associated with IQ and did not attenuate the crude association between childhood maltreatment and IQ. This suggests that childhood maltreatment and genetic liability for schizophrenia may be independently associated with poor cognitive functioning.

In conclusion, our findings suggest that two measures of genetic liability for psychosis (FH and SZ-PRS) cannot account for the lower levels of cognition found among adults maltreated in childhood. Future research should use large longitudinal studies to prospectively investigate the impact of genetic liability and childhood maltreatment on different stages of cognitive development. Presently, the reason why the association between childhood adversity and cognition in patients with a psychotic disorder is weaker than in controls remains to be elucidated.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00127-023-02513-0>.

Acknowledgements The European Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EU-GEI) WP2 Group members includes: Amoretti, Silvia, PhD, Barcelona Clinic Schizophrenia Unit, Hospital Clinic, Departament de Medicina, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB), Institut d'Investigacions Biomèdiques, August Pi I Sunyer (IDIBAPS), Barcelona, Spain; Centro de Investigación Biomédica en Red de Salud Mental CIBERSAM, Instituto de Salud Carlos III, Madrid, Spain; Andreu-Bernabeu, Álvaro, Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain; Baudin, Grégoire, MSc, AP-HP, Groupe Hospitalier “Mondor,” Pôle de Psychiatrie, Créteil, France, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France; Beards, Stephanie, PhD, Department of Health Service and Population Research, Institute of Psychiatry, King’s College London, London, England; Bonetto, Chiara, PhD, Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy; Bonora, Elena, PhD, Department of Medical and Surgical Science, Genetic Unit, Alma Mater Studiorum Università di Bologna, Bologna, Italy; Cabrera, Bibiana, MSc, PhD, Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, Hospital Clinic of Barcelona, Barcelona, Spain, CIBERSAM, Spain; Carracedo, Angel, MD, PhD, Fundación Pública Galega de Medicina Xenómica, Hospital Clínico Universitario, CIBERER, Santiago de Compostela, Spain; Charpeaud, Thomas, MD, Fondation Fondamental, Créteil, France, CMP B CHU, Clermont Ferrand, France, and Université Clermont

Auvergne, Clermont-Ferrand, France; Costas, Javier, PhD, Fundación Pública Galega de Medicina Xenómica, Hospital Clínico Universitario, Santiago de Compostela, Spain; Cristofalo, Dorian, MA, Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy; Cuadrado, Pedro, MD, Villa de Vallecas Mental Health Department, Villa de Vallecas Mental Health Centre, Hospital Universitario Infanta Leonor/Hospital Virgen de la Torre, Madrid, Spain; Durán-Cutilla, Manuel, MD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, Institute of Psychiatry and Mental Health, IISGM, School of Medicine, Universidad Complutense, Madrid, Spain; Ferchiou, Aziz, MD, AP-HP, Groupe Hospitalier “Mondor”, Pôle de Psychiatrie, Créteil, France, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France; Fraguas, David, MD, PhD, Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Barcelona, Spain; Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, Institute of Psychiatry and Mental Health, IISGM, School of Medicine, Universidad Complutense, Madrid, Spain; Franke, Nathalie, MSc, Department of Psychiatry, Early Psychosis Section, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; Frijda, Flora, MSc, Etablissement Public de Santé Maison Blanche, Paris, France; Garcia-Portilla, Paz, MD, PhD, Department of Medicine, Psychiatry Area, School of Medicine, Universidad de Oviedo, ISPA, INEUROPA, CIBERSAM, Oviedo, Spain; González Peñas, Javier, Hospital Gregorio Marañón, IISGM, School of Medicine, Madrid, Spain; Hubbard, Kathryn, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London; Jamain, Stéphane, PhD, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France, Faculté de Médecine, Université Paris-Est, Créteil, France, and Fondation Fondamental, Créteil, France; Jiménez-López, Estela, MSc, Department of Psychiatry, Servicio de Psiquiatría Hospital “Virgen de la Luz,” Cuenca, Spain; Leboyer, Marion, MD, PhD, AP-HP, Groupe Hospitalier “Mondor,” Pôle de Psychiatrie, Créteil, France, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France, Faculté de Médecine, Université Paris-Est, Créteil, France, and Fondation Fondamental, Créteil, France; Llorente, Cloe, MD, Department of Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, Investigación Sanitaria del Hospital Gregorio Marañón (CIBERSAM), Madrid, Spain; López Montoya, Gonzalo, PhD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM (CIBERSAM), Madrid, Spain; Lorente-Rovira, Esther, PhD, Department of Psychiatry, School of Medicine, Universidad de Valencia, CIBERSAM, Valencia, Spain; M Díaz-Caneja, Covadonga, Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain; Marcelino Loureiro, Camila, MD, Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, São Paulo, Brasil, and Núcleo de Pesquisa em Saúde Mental Populacional, Universidade de São Paulo, São Paulo, Brasil; Matteis, Mario, MD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM (CIBERSAM), Madrid, Spain; Messchaert, Elles, MSc, Rivierduinen Centre for Mental Health, Leiden, the Netherlands; Moltó, Ma Dolores, Department of Genetics, University of Valencia, Campus of Burjassot, Biomedical Research Institute INCLIVA, Valencia, Spain, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; Mezquida, Gisela, PhD, Barcelona Clinic Schizophrenia Unit, Hospital Clinic, Departament de Medicina, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB), Institut d’Investigacions Biomèdiques, August Pi I Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Salud Mental CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain; Moreno, Carmen, MD, Department of Psychiatry, Hospital General Universitario

Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM (CIBERSAM), Madrid, Spain; Muratori, Roberto, MD, Department of Mental Health and Pathological Addiction, Local Health Authority, Bologna, Italy; Nacher Juan, Neurobiology Unit, Department of Cell Biology, Interdisciplinary Research Structure for Biotechnology and Biomedicine (BIOTECMED), Universitat de València, Valencia, Spain, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); Spanish National Network for Research in Mental Health, Madrid, Spain, Fundación Investigación Hospital Clínico de Valencia, INCLIVA, Valencia, Spain; Parellada, Mara, MD, PhD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM (CIBERSAM), Madrid, Spain; Rapado-Castro, Marta, PhD, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, Institute of Psychiatry and Mental Health, IISGM, School of Medicine, Universidad Complutense, Madrid, Spain; Ruggeri, Mirella, MD, PhD, Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy; Richard, Jean-Romain, MSc, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France, and Fondation Fondamental, Créteil, France; Rodríguez Solano, José Juan, MD, Puente de Vallecas Mental Health Department, Hospital Universitario Infanta Leonor/Hospital Virgen de la Torre, Centro de Salud Mental Puente de Vallecas, Madrid, Spain; Sáiz, Pilar A, Department of Psychiatry, School of Medicine, University of Oviedo, CIBERSAM, Instituto de Neurociencias del Principado de Asturias, INEUROPA, Oviedo, Spain; Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain; Sánchez-Gutierrez, Teresa, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM, CIBERSAM, C/Doctor Esquerdo 46, 28007 Madrid, Spain. Faculty of Health Science. Universidad Internacional de La Rioja (UNIR), Madrid, Spain; Sánchez, Emilio, MD, Department of Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IISGM (CIBERSAM), Madrid, Spain; Schürhoff, Franck, MD, PhD, AP-HP, Groupe Hospitalier “Mondor,” Pôle de Psychiatrie, Créteil, France, Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France, Faculté de Médecine, Université Paris-Est, Créteil, France, and Fondation Fondamental, Créteil, France; Seri, Marco, MD, Department of Medical and Surgical Science, Genetic Unit, Alma Mater Studiorum Università di Bologna, Bologna, Italy; Shuhama, Rosana, PhD, Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, São Paulo, Brasil, and Núcleo de Pesquisa em Saúde Mental Populacional, Universidade de São Paulo, São Paulo, Brasil; Termorshuizen, Fabian, PhD, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, South Limburg Mental Health Research and Teaching Network, Maastricht University Medical Centre, Maastricht, the Netherlands, and Rivierduinen Centre for Mental Health, Leiden, the Netherlands; Tronche, Anne-Marie, MD, Fondation Fondamental, Créteil, France, CMP B CHU, Clermont Ferrand, France, and Université Clermont Auvergne, ClermontFerrand, France; van Dam, Daniella, PhD, Department of Psychiatry, Early Psychosis Section, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; van der Ven, Elsje, PhD, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, South Limburg Mental Health Research and Teaching Network, Maastricht University Medical Centre, Maastricht, the Netherlands, and Rivierduinen Centre for Mental Health, Leiden, the Netherlands.

Amoretti Silvia, Andreu-Bernabeu Álvaro, Baudin Grégoire, Beards Stephanie, Bonetto Chiara, Bonora Elena, Cabrera Bibiana, Carracedo Angel, Charpeaud Thomas, Costas Javier, Cristofalo Dorian, Cuadrado Pedro, Durán-Cutilla Manuel, Ferchiou Aziz, Fraguas David, Franke Nathalie, Frijda Flora, Llorente Cloe, Garcia-Portilla Paz, González Peñas Javier, Hubbard Kathryn, Jamain Stéphane,

Jiménez-López Estela, Leboyer Marion, López Montoya Gonzalo, Lorente-Rovira Esther, M. Díaz-Caneja Covadonga, Marcelino Loureiro Camila, Matteis Mario, Messchaert Elles, Moltó Ma Dolores, Mezquida Gisela, Moreno Carmen, Muratori Roberto, Nacher Juan, Parellada Mara, Rapado-Castro Marta, Ruggeri Mirella, Richard Jean-Romain, Rodríguez Solano José Juan, A. Sáiz Pilar, Sánchez-Gutiérrez Teresa, Sánchez Emilio, Schürhoff Franck, Seri Marco, Shuhama Rosana, Termorshuizen Fabian, Tronche Anne-Marie, van Dam Daniëlla, van der Ven Elsje

Author contributions DQ, DLB, CLC, LF, EV, GT, CG-A, SS, FS, CS, GM, AL, ST, IT, DB, GDA, CA, MA, MB, JB, JS, JLS, PMR, CMD-B, HEJ, PBJ, JBK, P-ML, AT, BP, LdH, J-PS, JvO, BPR, RB, MDF, RMM, CM, and all the authors in the EU-GEI group collected or supervised the data collection. LS did the data analysis and wrote the first draft of the manuscript. AF contributed to creation of the tables. MA and DQ assisted with the genetic analysis. All authors provided a careful methodological revision of the manuscript, contributed to and approved the final draft. CM and HLF have equally supervised this work and they are joint senior authors.

Funding We are grateful to the EU-GEI study participants for their essential contribution to this project. The EU-GEI Study is funded by grant agreement HEALTH-F2-2010–241909 (Project EU-GEI) from the European Community's Seventh Framework Programme, and Grant 2012/0417–0 from the São Paulo Research Foundation. B.P.F. Rutten is funded by a VIDI award (no. 91.718.336) from the Netherlands Scientific Organization. H. L. Fisher, C. Gayer-Anderson, and C. Morgan are supported by the Economic and Social Research Council (ESRC) Centre for Society and Mental Health at King's College London [ES/S012567/1]. D. Quattrone is supported by the Medical Research Council Clinical Academic Research Partnership [MR/W030608/1]. M. Aas is supported by an MRC fellowship (#MR/WO27720/1). C. Arango has received support from the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (ISCIII), co-financed by the European Union, ERDF Funds from the European Commission, "A way of making Europe", financed by the European Union—NextGenerationEU (PMP21/00051, PI19/01024), CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds, European Union Seventh Framework Program, European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking: Project PRISM-2 (Grant agreement No.101034377), Project AIMS-2-TRIALS (Grant agreement No 777394), Horizon Europe, the National Institute of Mental Health of the National Institutes of Health under Award Number 1U01MH124639-01 (Project ProNET) and Award Number 5P50MH115846-03 (Project FEP-CAUSAL), Fundación Familia Alonso, and Fundación Alicia Koplowitz. The views expressed are those of the authors and not necessarily those of the ESRC or King's College London.

Declarations

Conflict of interest Prof. Morgan is the Editor-in-Chief of this journal. Dr. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda. The other authors have declared that there are no conflicts of interest in relation to the subject of this study.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing,

adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Vargas T, Lam PH, Azis M et al (2019) Childhood trauma and neurocognition in adults with psychotic disorders: a systematic review and meta-analysis. *Schizophr Bull* 45:1195–1208
2. Sideli L, Schimmenti A, La Barbera D et al (2022) Childhood maltreatment, educational attainment, and IQ: findings from a multicentric case-control study of first-episode psychosis (EU-GEI). *Schizophr Bull* 48:575–589. <https://doi.org/10.1093/schbul/sbac004>
3. Aas M, Djurovic S, Athanasios L et al (2012) Serotonin transporter gene polymorphism, childhood trauma, and cognition in patients with psychotic disorders. *Schizophr Bull* 38:15–22. <https://doi.org/10.1093/schbul/sbr113>
4. Aas M, Haukvik UK, Djurovic S et al (2013) BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses. *Prog Neuro-Psychopharmacol Biol Psychiatry* 46:181–188. <https://doi.org/10.1016/j.pnpbp.2013.07.008>
5. Green MJ, Chia TY, Cairns MJ et al (2014) Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *J Psychiatr Res* 49:43–50. <https://doi.org/10.1016/j.jpsychires.2013.10.018>
6. Green MJ, Raudino A, Cairns MJ et al (2015) Do common genotypes of FK506 binding protein 5 (FKBP5) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls? *J Psychiatr Res* 70:9–17. <https://doi.org/10.1016/j.jpsychires.2015.07.019>
7. Danese A, Moffitt TE, Arseneault L et al (2017) The origins of cognitive deficits in victimized children: implications for neuroscientists and clinicians. *Am J Psychiatry* 174:349–361. <https://doi.org/10.1176/appi.ajp.2016.16030333>
8. van Os J, Marsman A, van Dam D et al (2017) Evidence that the impact of childhood trauma on IQ is substantial in controls, moderate in siblings, and absent in patients with psychotic disorder. *Schizophr Bull* 43:316–324. <https://doi.org/10.1093/schbul/sbw177>
9. van Os J, van Der Steen Y, Islam MA et al (2017) Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychol Med* 47:2421–2437. <https://doi.org/10.1017/S0033291717000915>
10. Santesteban-Echarri O, Sandel D, Liu L et al (2022) Family history of psychosis in youth at clinical high risk: a replication study. *Psychiatry Res* 311:114480. <https://doi.org/10.1016/j.psychres.2022.114480>
11. Murray GK, Lin T, Austin J et al (2021) Could polygenic risk scores be useful in psychiatry? A review. *JAMA Psychiat* 78:210–219. <https://doi.org/10.1001/jamapsychiatry.2020.3042>
12. Wray NR, Lin T, Austin J et al (2021) From basic science to clinical application of polygenic risk scores: a primer. *JAMA Psychiat* 78:101–109. <https://doi.org/10.1001/jamapsychiatry.2020.3049>

13. Van Os J, Pries LK, Delespaul P et al (2020) Replicated evidence that endophenotypic expression of schizophrenia polygenic risk is greater in healthy siblings of patients compared to controls, suggesting gene-environment interaction. The EUGEI study Psychol Med 50:1884–1897. <https://doi.org/10.1017/S003329171900196X>
14. Hubbard L, Tansey KE, Rai D et al (2016) Evidence of common genetic overlap between schizophrenia and cognition. Schizophr Bull 42:832–842. <https://doi.org/10.1093/schbul/sbv168>
15. Hagenaars SP, Harris SE, Davies G et al (2016) Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia. Mol Psychiatry 21:1624–1632. <https://doi.org/10.1038/mp.2015.225>
16. Legge SE, Cardno AG, Allardyce J et al (2021) Associations between schizophrenia polygenic liability, symptom dimensions, and cognitive ability in schizophrenia. JAMA Psychiatr 78:1143–1151. <https://doi.org/10.1001/jamapsychiatry.2021.1961>
17. Richards AL, Pardiñas AF, Frizzati A et al (2020) The relationship between polygenic risk scores and cognition in Schizophrenia. Schizophr Bull 46:336–344. <https://doi.org/10.1093/schbul/sbz061>
18. Lencz T, Knowles E, Davies G et al (2014) Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics Consortium (COGENT). Mol Psychiatry 19:168–174. <https://doi.org/10.1038/mp.2013.166>
19. Woolway GE, Smart SE, Lynham AJ et al (2022) Schizophrenia polygenic risk and experiences of childhood adversity: a systematic review and meta-analysis. Schizophr Bull 48:967–980. <https://doi.org/10.1093/schbul/sbac049>
20. Van Os J, Rutten BPP, Myin-Germeys I et al (2014) Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull 40:729–736. <https://doi.org/10.1093/schbul/sbu069>
21. Gayer-Anderson C, Jongsma HE, Di Forti M et al (2020) The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI): incidence and First-Episode Case-Control Programme. Soc Psychiatry Psychiatr Epidemiol 55:645–657. <https://doi.org/10.1007/s00127-020-01831-x>
22. Jongsma HE, Gayer-Anderson C, Lasalvia A et al (2018) Treated incidence of psychotic disorders in the multinational EU-GEI study. JAMA Psychiatr 75:36–46. <https://doi.org/10.1001/jamapsychiatry.2017.3554>
23. Blyler CR, Gold JM, Iannone VN, Buchanan RW (2000) Short form of the WAIS-III for use with patients with schizophrenia. Schizophr Res 46:209–215. [https://doi.org/10.1016/S0920-9964\(00\)00017-7](https://doi.org/10.1016/S0920-9964(00)00017-7)
24. Velthorst E, Levine SZ, Henquet C et al (2013) To cut a short test even shorter: reliability and validity of a brief assessment of intellectual ability in Schizophrenia—a control-case family study. Cogn Neuropsychiatry 18:574–593. <https://doi.org/10.1080/13546805.2012.731390>
25. Velthorst E, Mollon J, Murray RM et al (2021) Cognitive functioning throughout adulthood and illness stages in individuals with psychotic disorders and their unaffected siblings. Mol Psychiatry 26(8):4529–4543. <https://doi.org/10.1038/s41380-020-00969-z>
26. NIMH Genetics Initiative (1992) Family interview for genetic studies (FIGS). National Institute of Mental Health, Rockville
27. Quattrone D, Reininghaus U, Richards AL et al (2021) The continuity of effect of schizophrenia polygenic risk score and patterns of cannabis use on transdiagnostic symptom dimensions at first-episode psychosis: findings from the EU-GEI study. Transl Psychiatry 11:1–10. <https://doi.org/10.1038/s41398-021-01526-0>
28. Ferraro L, Quattrone D, La Barbera D et al (2022) First-episode psychosis patients who deteriorated in the premorbid period do not have higher polygenic risk scores than others: a cluster analysis of EU-GEI data. Schizophr Bull. <https://doi.org/10.1093/schbul/sbac100>
29. Tripoli G, Quattrone D, Ferraro L et al (2022) Facial emotion recognition in psychosis and associations with polygenic risk for schizophrenia: findings from the multi-center EU-GEI case-control study. Schizophr Bull 48:1104–1114. <https://doi.org/10.1093/schbul/sbac022>
30. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L (1997) Validity of the childhood trauma questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 36:340–348. <https://doi.org/10.1097/00004583-199703000-00012>
31. Trotta A, Di FM, Iyegbe C et al (2015) Familial risk and childhood adversity interplay in the onset of psychosis. BJPsych Open 1:6–13. <https://doi.org/10.1192/bjpo.bp.115.000158>
32. Fisher HL, McGuffin P, Boydell J et al (2014) Interplay between childhood physical abuse and familial risk in the onset of psychotic disorders. Schizophr Bull 40:1443–1451. <https://doi.org/10.1093/schbul/sbt201>
33. van Winkel R, van Nierop M, Myin-Germeys I, van Os J (2013) Childhood trauma as a cause of psychosis: linking genes, psychology, and biology. Can J Psychiatry 58:44–51
34. Sideli L, Murray RM, Schimmenti A et al (2020) Childhood adversity and psychosis: a systematic review of bio-psycho-social mediators and moderators. Psychol Med 50:1761–1782. <https://doi.org/10.1017/S0033291720002172>

Authors and Affiliations

Lucia Sideli^{1,2,3} · Monica Aas^{2,4,5,6} · Diego Quattrone⁴ · Daniele La Barbera³ · Caterina La Cascia³ · Laura Ferraro³ · Luis Alameda^{2,7,8,9} · Eva Velthorst¹⁰ · Giulia Trotta² · Giada Tripoli^{1,2,3,11} · Adriano Schimmenti¹² · Andrea Fontana¹ · Charlotte Gayer-Anderson^{13,14} · Simona Stilo^{2,15} · Fabio Seminerio³ · Crocettarachele Sartorio³ · Giovanna Marrazzo³ · Antonio Lasalvia¹⁶ · Sarah Tosato¹⁶ · Ilaria Tarricone¹⁷ · Domenico Berardi¹⁸ · Giuseppe D'Andrea¹⁸ · EU-GEI WP2 Group · Celso Arango¹⁹ · Manuel Arrojo²⁰ · Miguel Bernardo^{21,22} · Julio Bobes²³ · Julio Sanjuán²⁴ · Jose Luis Santos²⁵ · Paulo Rossi Menezes²⁶ · Cristina Marta Del-Ben²⁷ · Hannah E. Jongsma^{28,29} · Peter B. Jones^{30,31} · James B. Kirkbride²⁸ · Pierre-Michel Llorca³¹ · Andrea Tortelli³² · Baptiste Pignon^{33,34,35} · Lieuwe de Haan³⁶ · Jean-Paul Selten^{37,38} · Jim Van Os^{2,38,39} · Bart P. Rutten³⁸ · Richard Bentall⁴⁰ · Marta Di Forti⁴ · Robin M. Murray² · Craig Morgan^{13,14} · Helen L. Fisher^{4,14}

✉ Lucia Sideli
l.sideli@lumsa.it

¹ Department of Human Science, LUMSA University, Piazza delle Vaschette, 101, 00193 Rome, Italy

- 2 Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, England
- 3 Department of Biomedicine, Neuroscience, and Advanced Diagnostic, University of Palermo, Palermo, Italy
- 4 Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England
- 5 NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, Oslo, Norway
- 6 Department of Behavioural Sciences, OsloMet, Oslo Metropolitan University, Oslo, Norway
- 7 Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Seville, Spain
- 8 Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, Departamento de Psiquiatría, Universidad de Sevilla, Seville, Spain
- 9 Service of General Psychiatry, Treatment and Early Intervention in Psychosis Program, Lausanne University Hospital (CHUV), Lausanne, Switzerland
- 10 Department of Research, Mental Health Service Organization 'GGZ Noord-Holland-Noord', Hoorn, The Netherlands
- 11 Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy
- 12 Faculty of Human and Social Sciences, UKE - Kore University of Enna, Enna, Italy
- 13 Department of Health Services and Population Research, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, England
- 14 ESRC Centre for Society and Mental Health, King's College London, London, UK
- 15 Department of Mental Health and Addiction Services, ASP Crotone, Crotone, Italy
- 16 Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
- 17 Department of Medical and Surgical Sciences, Alma Mater Studiorum - Bologna University, Bologna, Italy
- 18 Department of Biomedical and NeuroMotor Sciences, Psychiatry Unit, Alma Mater Studiorum - Bologna University, Bologna, Italy
- 19 Institute of Psychiatry and Mental Health, Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, ISGM, CIBERSAM, Madrid, Spain
- 20 Department of Psychiatry, Psychiatric Genetic Group, Instituto de Investigación Sanitaria de Santiago de Compostela, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago, Spain
- 21 Barcelona Clinic Schizophrenia Unit, Hospital Clinic, Departament de Medicina, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB), Institut d'Investigacions Biomèdiques, August Pi I Sunyer (IDIBAPS), Barcelona, Spain
- 22 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
- 23 Department of Medicine, Psychiatry Area, School of Medicine, Universidad de Oviedo, ISPA, INEUROPA, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, Spain
- 24 Department of Psychiatry, School of Medicine, Universidad de Valencia, Centro de Investigación Biomédica en Red de Salud Mental, Valencia, Spain
- 25 Department of Psychiatry, Hospital "Virgen de La Luz", Cuenca, Spain
- 26 Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil
- 27 Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, São Paulo, Brazil
- 28 PsyLife Group, Division of Psychiatry, University College London, London, England
- 29 Department of Psychiatry, University of Cambridge, Cambridge, England
- 30 CAMEO Early Intervention Service, Cambridgeshire and Peterborough National Health Service Foundation Trust, Cambridge, England
- 31 EA 7280 Npsydo, Université Clermont Auvergne, Clermont-Ferrand, France
- 32 Etablissement Public de Santé, Maison Blanche, Paris, France
- 33 AP-HP, Groupe Hospitalier "Mondor", Pôle de Psychiatrie, Créteil, France
- 34 Institut National de la Santé et de la Recherche Médicale, U955, Créteil, France
- 35 Fondation FondaMental, Créteil, France
- 36 Early Psychosis Section, Department of Psychiatry, Amsterdam UMC, Amsterdam, The Netherlands
- 37 Institute for Mental Health, GGZ Rivierduinen, Leiden, The Netherlands
- 38 Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands
- 39 Department Psychiatry, Utrecht University Medical Centre, Utrecht, The Netherlands
- 40 Department of Psychology, University of Sheffield, Cathedral Court, 1 Vicar Lane, Sheffield S1 2LT, UK