

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Childhood medical history and psychosis in adult life: Findings from the Bologna EU-GEI incidence and case-control study

This is the submitted version (pre peer-review, preprint) of the following publication:

Published Version:

D'Andrea G., Suprani F., Tolomelli E., Gennari M., Lanari M., Faldella G., et al. (2021). Childhood medical history and psychosis in adult life: Findings from the Bologna EU-GEI incidence and case-control study. *EARLY INTERVENTION IN PSYCHIATRY*, 15(2), 397-401 [10.1111/eip.12970].

Availability:

This version is available at: <https://hdl.handle.net/11585/809496> since: 2021-02-28

Published:

DOI: <http://doi.org/10.1111/eip.12970>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the submitted version of:

Childhood medical history and psychosis in adult life: Findings from the Bologna EU-GEI incidence and case-control study

G. D'Andrea, F. Suprani, E. Tolomelli, M. Gennari, M. Lanari, G. Faldella, R. Muratori, D. Berardi, I. Tarricone

Early Intervention in Psychiatry 2021, 15(2)

The final published version is available online at:

<https://doi.org/10.1111/eip.12970>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Childhood medical history and psychosis in adult life

Findings from the Bologna EU-GEI incidence and case-control study

Giuseppe D'Andrea, MD,¹ * Federico Suprani, MD,² Elena Tolomelli, MD,² Monia Gennari, MD, PhD³ Marcello Lanari, MD³ Giacomo Faldella, MD³ Roberto Muratori, MD,⁴ Domenico Berardi, MD,^{1 4} Ilaria Tarricone, MD, PhD,^{2 4}

¹ Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

² Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

³ Pediatric Emergency Unit, Department of Medical and Surgical Sciences (DIMEC), St. Orsola-Malpighi University Hospital, Bologna, Italy

⁴ Department of Mental Health, AUSL Bologna, Bologna, Italy

*Corresponding Author: Giuseppe D'Andrea, Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Via Ugo Foscolo 7, 40123, Bologna, Italy. *E-mail address:* giuseppe.dandrea6@studio.unibo.it *Tel.:* +39 3484679232

Word count: 1.582 words.

Abstract

Objective

We aimed to investigate the relation between childhood medical history and psychosis onset in adult life.

Methods

We conducted a retrospective case-control study of first-episode psychosis (FEP) incident cases to evaluate if a history of pediatric hospitalizations or Emergency Room (ER) visits for non-psychiatric reasons could increase the odds of FEP in adult life. Seventy patients aged 18-64 with a diagnosis of FEP (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes F20-F33) confirmed by the Operational Criteria Checklist, between May 2010 and April 2015, and 65 controls without FEP recruited in the same catchment area. We calculated odds ratios for incident FEP associated with hospital admissions and ER visits prior to age of 18, adjusted for demographic factors and other confounders.

Results

In multivariable logistic regression analysis risk of FEP increased significantly if the participant had a childhood/adolescence history of at least one hospital admission ($p=.01$) or one ER visit ($p<.001$). The association remained significant adjusting for socio-demographic factors, cannabis use and trauma history.

Conclusions

A robust association between hospitalizations before age of 18 and FEP was observed. Children and adolescents with this clinical history may be at very high risk of psychotic disorders. Further studies with a prospective design and a larger sample are needed to confirm this association.

Keywords: first-episode psychosis, pediatric hospitalization, pediatric health

1. Introduction

Psychosis seems to be determined by the interaction of genetic and environmental factors [1]. For the majority of the latter, the increase in risk is associated with exposure during childhood and adolescence. The association between childhood adversity and trauma and psychosis has been largely investigated [2]. Nevertheless, childhood medical history has not been investigated as a psychosis risk factor. In our knowledge only one prior case-control study investigated the relationship between pediatric general health and psychosis in adult life; this study found that severe injuries during adolescence may predict later onset of first-episode psychosis (FEP) [3].

We conducted a case-control study of FEP incidence cases to evaluate if a history of pediatric hospitalizations or ER visits for any non-psychiatric medical reason could increase the odds of FEP in adult life.

2. Materials and methods

2.1 Sampling

The study population was extrapolated from the subjects recruited for the incidence and case-control EU-GEI study (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al., 2014) in 5 Community Mental Health Centres (CMHCs) in Bologna, Italy. Ethical approval was obtained from the local research ethics committee (protocol No 113/2006/U/Sper) and written consent was obtained from those who agreed to participate in the case-control study. Full sampling methods and detailed inclusion criteria for cases are reported elsewhere [4]. Healthy controls were recruited with quota-based strategy in the same time span and catchment area. Inclusion criteria for controls were: 18 to 64 years of age and residency within the catchment area. Individuals who had history of previous psychotic episode or had received any treatment with antipsychotic medications were excluded.

2.2 Measures and data collection

Our primary outcome was *ICD-10* diagnosis of psychotic disorder (*ICD-10* codes F20-F33) confirmed by

OPCRIT system [5].

We collected data about parental social class (European Socio-Economic Classification, ESEC) [6], family history of psychosis, cannabis use, and child maltreatment (Childhood Trauma Questionnaire, CTQ) [7].

Health system electronic records of the main Bologna- hospitals were used to retrospectively collect inpatient admissions and ER accesses, including admission and discharge date and diagnosis, occurred between age 0-11 (childhood) and 12-17 (adolescence).

2.3 Statistics

Statistical analyses were carried out using SPSS 23.0 for Windows.

First, descriptive and inferential statistics were performed using statistics test for categorical and quantitative variables as appropriate.

Finally, we calculated unadjusted Odds Ratios (OR) for the variables and then we fitted a series of logistic regression models to investigate the association between childhood and adolescence clinical history and case-control status, with sequential adjustment as follows:

- Crude (univariable) association between FEP (case-control) status and pediatric clinical history variables (hospital admission and ER visit before 18 years of age)
- Model A: adjusted for age, sex, migrant status, and cannabis use
- Model B. Model A + parental SES and CTQ

3. Results

3.1 Description of the study population

Our sample included 135 participants: 51.8% (n=70) were cases who received diagnosis of FEP, and 48.2% (n=65) were healthy controls. The sample characteristics are described in *Table 1*.

3.2 ER accesses and Hospitalizations

We found records of 53 ER visits for cases and 13 for controls. The total number of hospital admissions was

27 for cases and 7 for controls.

Patients with FEP later in life ($n=19$; 27.1%) were more likely than controls ($n=3$; 4.6%) to have had at least one ER visit ($p<.001$). Seventeen percent of the cases ($n=12$) had a clinical history of two or more ER accesses, compared to 3.1% ($n=2$) of the controls ($p=.01$).

Twenty percent of the individuals who would later develop FEP ($n=14$) underwent hospitalization at least once before the age of 18 years, opposed to 6.2% ($n=4$) of the controls ($p=.02$).

Ten percent ($n=7$) of the cases had a history of two or more hospitalizations, compared to 1.5% ($n=1$) in the control group ($p=.06$).

If we considered the 2 separate age groups, only during adolescence the difference of both ER accesses and hospitalizations between cases and controls was statistically significant ($p=.002$).

3.4 Odds ratios

Both having been admitted at least once ($OR=7.69$; 95% CI 2.16-27.49; $p=.002$) or multiple times ($OR=6.52$; 95% CI 1.39-30.37; $p=.02$) to ER before age of 18 increased the odds of FEP later in life. Having been hospitalized before age of 18 was significantly correlated to FEP ($OR=3.81$; 95% CI 1.19-12.27; $p=.03$) (*Table 2*); having been hospitalized multiple times before age of 18 showed a trend for statistically significant correlation with FEP in adult life ($OR=7.11$; 95% CI 0.85-59.48; $p=.07$).

When we considered the 2 separated age groups, only during adolescence ER visits and hospitalizations were associated with an increase in the OR of FEP (respectively: $OR=6.12$, 95% CI 1.69-22.16, $p=.006$ for ER accesses; $OR=13.24$, 95% CI 1.67-105.01, $p=.01$ for hospitalizations).

Finally, we calculated adjusted OR for both having been hospitalized (*Table 2*) and having accessed ER (*Table 2*) prior to the onset of FEP. In Model A, having been admitted to hospital at least once before age of 18 increased almost fourfold the odds of later being diagnosed with FEP ($OR=4.58$; 95% CI 1.31-15.95; $p=.02$), while having accessed the ER at least once before age of 18 was associated with an fourteenfold increase in the odds of having a first-episode psychosis ($OR=14.47$; 95% CI 3.58-58.59; $p<.001$).

Finally, adding parental social class and CTQ to the model brought to an increase in the odds of FEP after

hospitalization (OR=6.07; 95% CI 1.48- 24.89; $p=.01$) or ER access (OR=20.16; 95% CI 3.88-104.59; $p<.001$) before age of 18.

Also, when we considered the effect of more than one ER access or hospitalization, we found a statistically significant increase of the odds of FEP (data available on request).

4. Discussion

The main finding of this study is that hospital admissions or ER accesses before the age of 18 years may predict FEP in adult life. The risk is higher if hospital admissions or ER accesses occurred during adolescence. Neither SES, migration, cannabis use or childhood trauma explain this association.

To our knowledge, this is the first investigations of the correlation between paediatric clinical history and FEP in adult life.

Our study is based on an incidence study capturing all potential FEP cases who contacted mental health services within the catchment area and leakage studies were conducted to minimize under-ascertainment [8]. The information about medical history (hospitalizations and ER accesses) were collected retrospectively; recall bias has been minimized using also digital records of both hospitalizations and ER accesses. When data were not available in the informatic registry we searched for the paper medical records in the inpatient unit archives. Contacts with other hospitals out of our catchment area could not be registered. Migrants' clinical history data availability depended on the age at migration.

One previous study [3] found that severe injuries during adolescence predict FEP. In our study we broadened the investigation to all medical circumstances which led to ER access or hospitalization before age of 18 and we found a strong association between pediatric clinical history and FEP in adult life.

An emerging conceptual model describes schizophrenia as a systemic developmental disorder characterized by mental and general health vulnerabilities [9], such as inflammation and immune system disorders [10,11], multiple metabolic and endocrine abnormalities, and autonomic nervous system dysfunctions. Finally, somatic complaints, such as unspecific pain, gastro-intestinal complaints, and neurological symptoms are common in early-stage psychosis [12,13] and may lead to repetitive healthcare-seeking behavior. In this perspective,

hospitalizations may be a prodromal sign of an emerging psychotic disorder. Our finding that the association between pediatric clinical history and FEP in adult life is more significant when hospitalizations/ER accesses have been occurred during adolescence reinforce the interpretation of the pediatric medical history as the “tip of the iceberg” of an emerging psychosis.

In our study, hospitalizations and ER accesses predicted later FEP independently from both socio- economic class and child maltreatment, and these results seem rule out the hypothesis that the increase in hospitalizations or ER accesses before age of 18 is a proxy of other known risk factors of psychosis, such as low socio-economic status or childhood trauma.

5. Conclusions

We found that hospitalizations and ER accesses before age of 18 are associated with later FEP. The findings of our study suggest that non-primary healthcare services may represent potential sites for early detection of psychotic disorders. Further studies with a larger sample are needed to confirm this association.

Acknowledgements

We acknowledge the contribution of Dr. Craig Morgan and Prof. Robin Murray, leaders of the Working Package 2 of the EU-GEI Project funded by the European Community (European Network of National Schizophrenia Networks Studying Gene Environment Interactions Project EU-GEI European Community’s Seventh Framework Program, grant agreement No. HEALTH-F2-2009-241909). WP2 allowed us to implement the EU-GEI research tools in the present project. We also deeply thank Dr. Marta Di Forti for her suggestions: her help was crucial in developing the Bologna EU-GEI study. We acknowledge the contribution of the entire Bologna - FEP Study team. We wish to thank the patients and clinical staff of the Bologna-CMHCs.

Conflict of Interest

The authors have no competing interests to report.

Funding

The EU-GEI Project was funded by the European Community (European Network of National Schizophrenia Networks Studying Gene Environment Interactions Project EU-GEI European Community's Seventh Framework Program, grant agreement No. HEALTH-F2-2009-241909).

References

- [1] M.T. Tsuang, J.L. Bar, W.S. Stone, S. V Faraone, Gene-environment interactions in mental disorders., *World Psychiatry*. 3 (2004) 73–83. <http://www.ncbi.nlm.nih.gov/pubmed/16633461> (accessed December 29, 2018).
- [2] F. Varese, F. Smeets, M. Drukker, R. Lieverse, T. Lataster, W. Viechtbauer, J. Read, J. van Os, R.P. Bentall, Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies., *Schizophr. Bull.* 38 (2012) 661–71. doi:10.1093/schbul/sbs050.
- [3] S. Luoma, H. Hakko, M. Marttunen, A. Taanila, S. Lindeman, Severe injuries in adolescence predict psychosis: A nested case control study of the Northern Finland 1966 Birth Cohort, *Schizophr. Res.* 118 (2010) 48–53. doi:10.1016/j.schres.2009.12.031.
- [4] H.E. Jongsma, C. Gayer-Anderson, A. Lasalvia, D. Quattrone, A. Mulè, A. Szöke, J.-P. Selten, C. Turner, C. Arango, I. Tarricone, D. Berardi, A. Tortelli, P.-M. Llorca, L. de Haan, J. Bobes, M. Bernardo, J. Sanjuán, J.L. Santos, M. Arrojo, C.M. Del-Ben, P.R. Menezes, E. Velthorst, R.M. Murray, B.P. Rutten, P.B. Jones, J. van Os, C. Morgan, J.B. Kirkbride, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package 2 (EU-GEI WP2) Group, Treated Incidence of Psychotic Disorders in the Multinational EU-GEI Study, *JAMA Psychiatry*. 75 (2018) 36. doi:10.1001/jamapsychiatry.2017.3554.
- [5] J. Williams, A.E. Farmer, M. Ackenheil, C.A. Kaufmann, P. McGuffin, T.O.R.R. Group, A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system, *Psychol. Med.* 26 (1996) 775. doi:10.1017/S003329170003779X.

- [6] D. Rose, E. Harrison, The European Socio-Economic Classification: A new social class schema for comparative European research, *Eur. Soc.* 9 (2007) 459–490. doi:10.1080/14616690701336518.
- [7] D.P. Bernstein, J.A. Stein, M.D. Newcomb, E. Walker, D. Pogge, T. Ahluvalia, J. Stokes, L. Handelsman, M. Medrano, D. Desmond, W. Zule, Development and validation of a brief screening version of the Childhood Trauma Questionnaire., *Child Abuse Negl.* 27 (2003) 169–90.
<http://www.ncbi.nlm.nih.gov/pubmed/12615092> (accessed January 9, 2019).
- [8] I. Tarricone, S. Mimmi, A. Paparelli, E. Rossi, E. Mori, S. Panigada, G. Carchia, V. Bandieri, R. Michetti, G. Minenna, J. Boydell, C. Morgan, D. Berardi, First-episode psychosis at the West Bologna Community Mental Health Centre: results of an 8-year prospective study, *Psychol. Med.* 42 (2012) 2255–2264. doi:10.1017/S0033291712000335.
- [9] B. Kirkpatrick, B. Miller, C. García-Rizo, E. Fernandez-Egea, Schizophrenia, *Clin. Schizophr. Relat. Psychoses.* 8 (2014) 73–79. doi:10.3371/CSRP.KIMI.031513.
- [10] G.M. Khandaker, L. Cousins, J. Deakin, B.R. Lennox, R. Yolken, P.B. Jones, Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment., *The Lancet. Psychiatry.* 2 (2015) 258–270. doi:10.1016/S2215-0366(14)00122-9.
- [11] G.M. Khandaker, R. Dantzer, P.B. Jones, Immunopsychiatry: important facts., *Psychol. Med.* 47 (2017) 2229–2237. doi:10.1017/S0033291717000745.
- [12] M.K. Rimvall, C.P. Jespersen, L. Clemmensen, A. Munkholm, A.M. Skovgaard, F. Verhulst, J. van Os, C.U. Rask, P. Jeppesen, Psychotic experiences are associated with health anxiety and functional somatic symptoms in preadolescence, *J. Child Psychol. Psychiatry.* (2018). doi:10.1111/jcpp.12986.
- [13] G. Stanghellini, M. Ballerini, P. Fusar Poli, J. Cutting, Abnormal Bodily Experiences May be a Marker of Early Schizophrenia?, *Curr. Pharm. Des.* 18 (2012) 392–398. doi:10.2174/138161212799316181.

Tables

Table 1

Sample characteristics.

Variables	Patients (N=70)	Controls (N=65)	P
Age	38.76 (SD 10.99)	40.51 (SD 12.46)	.388 ^a
Sex (Male)	50% (n=35)	36.9% (n=24)	.165 ^b
Parental Social Class			
Unemployed	0% (n=0)	1.6% (n=1)	
Working Class	41.9% (n=26)	27.9% (n=17)	.884 ^c
Intermediate	20.9% (n=13)	31.1% (n=19)	
Salariat	37.1% (n=23)	39.3% (n=24)	
Family History of Psychosis	9.1% (n=6)	7.1% (n=4)	.752 ^c
Migrant (Yes)	27.1% (n=19)	9.2% (n=6)	.008 ^b
Life-Time Cannabis Use	50% (n=35)	52.3% (n=34)	.864 ^c
Child Maltreatment ^d	47.1% (n=35)	47.8% (n=33)	.728 ^b

^a p-value was calculated with t-test

^b p-value was calculated with chi-square test

^c p-value was calculated with Fisher's exact test

^d CTQ total score was cut-off by the median

Table 2

Odds Ratios for pediatric clinical history variables and FEP.

Variable	Unadjusted OR (95%CI)	Model A ¹ OR (95%CI)	Model B ² OR (95%CI)
Hospital admission Yes vs No	3.81 (1.19-12.27)	4.58 (1.31-15.95)	6.07 (1.48-24.89)
ER visit Yes vs No	7.69 (2.16-27.49)	14.47 (3.58-58.49)	20.2 (3.88-104.59)

¹: Model A is adjusted for covariates (sex, migrant status, and cannabis use)

²: Model B is further adjusted for parental social class and childhood trauma

Odds ratios in **bold** are significant (p<.05)