**Supplementary Information**

**Structural brain abnormalities in schizophrenia in adverse environments: examining the effect of poverty and violence in six Latin American cities.**

N. A. Crossley, A. Zugman, F. Reyes-Madrigal, L. S. Czepielewski, M. N. Castro, A. M. Diaz-Zuluaga, J. A. Pineda-Zapata, R. Reckziegel, A. Gadelha, A. Jackowski, C. Noto, L. M. Alliende, B. Iruretagoyena, T. Ossandon, J. P. Ramirez-Mahaluf, C. P. Castañeda, A. Gonzalez-Valderrama, R. Nachar, P. León-Ortiz, J. Undurraga, C. López-Jaramillo, S. Guinjoan, C. S. Gama, C. de la Fuente-Sandoval, R. A. Bressan, for the ANDES Network.

- **Supplementary Results:**

* Exploring the role of shared variance in environmental factors.
* Confirmatory analysis correcting for inter-scan variability using mixed-models.
* Effect of chronicity and gender on the interaction between income and disease on total grey matter volume.

- **Supplementary Figure:**

* Figure S1: Differential effect of income and case on total grey matter volume according to chronicity of the disease and gender.
* Figure S2: Effect of income on total grey matter volume across different cities.
* Figure S3: Total grey matter volume and neighborhood violence in patients and controls.

- **Supplementary Tables:**

* Table S1: Characteristics of the cohorts included.

**Supplementary Results**

**Exploring the role of shared variance in environmental factors.**

As described in the main text, income and homicide rates were significantly correlated. To explore the effect of this shared variance in our main result, we repeated the analyses of the association of total grey matter volume but only considering one of these factors at the time in the analyses (alongside the variables of no interest of gender and age):

* The model including income and income x case showed a significant association of income x case in the same direction as the main analysis reported in the manuscript: ß= -447.4+/-193.7, *P*=0.02.
* The model including violence and violence x case did not show a significant association with either of these two variables.

As such, our main result of the effect of income in total grey matter volume does not change when including only one of these variables at the time.

**Confirmatory analysis correcting for inter-scan variability using mixed-models.**

Our study included images acquired in different scanners, which implied having to deal with variability between-scanners using ComBat. We also performed the analysis of total grey matter and environmental factors using a mixed-model approach, in which scanner was considered in our model a random effect. Alongside scanner, we included as fixed-effects the exact same factors as in our main analysis (case, income, income x case, violence, violence x case, age and gender). Including scanner as a random effect is similar to the ENIGMA initiative approach, which uses a random-effect analyses but on summary (meta-analysis) data (average and variance of each site).

Our results using a mixed-model were very similar to our reported results:

- the interaction between income x case and total grey matter volume was significant, with a ß= -559.8+/-209.1, and *P* value of 0.008.

- a trend-level significance in the association between grey matter volume and violence x case, with a ß=-394.8+/-204.8, P=0.054).

**Effect of chronicity and gender on the interaction between income and disease on total grey matter volume.**

We also performed a statistical analysis looking at the effect of chronicity and gender in the interaction between income and case on total grey matter volume. This analysis complements the visual impression from Figure S1, which shows that the direction of the effect is similar. We included a three-way interaction term for age (case x income x age) in the linear model used, where age was a measure of chronicity of the disorder. We found that this term was non-significant (*P*=0.97). Its inclusion did not improve the fit of the overall linear model according to Akaike’s criterion either. Similarly, we ran a separate model adding an interaction term including gender (case x income x gender), but the new interaction term was non-significant either (*P*=0.94) and did not improve the overall fit. Thus, we conclude that there is no evidence from our data that the case x income differential effect is seen only in one gender or in a specific stage of the disease.

**Supplementary Figures**

Figure S1



**Figure S1. Differential effect of income on total grey matter volume according to chronicity of the disease and gender.** A) Effect of income in controls and patients in sites recruiting first episodes exclusively (FEP) and rest of sites (Non-FEP). B) Effect of income in male controls and patients, and female controls and patients. In both situations, the direction of the effect is maintained. Supplementary Results describe the statistical analysis showing the lack of evidence that these two factors play a role in the observed effect.

Figure S2



**Figure S2. Effect of income on total grey matter volume across different cities.** Note that the direction of the relationship is consistent across cities except Sao Paulo. Mexico City did not show a negative effect of income on patients as in most other cohorts. However, most patients recruited were from highly deprived setting, with little variance observed to explore correlations. Considering the moderate correlation observed across sites, it is not surprising that within the smaller individual cities the correlations were non-significant, except for the association between income and grey matter in patients in Buenos Aires.

Figure S3

|  |  |
| --- | --- |
|  |  |

**Figure S3. Total grey matter volume and neighbourhood violence in patients and controls.** Total grey matter volume and neighbourhood’s homicide rates were negatively correlated in patients, but not controls. This might suggest that patients’ brains are more vulnerable to environmental violence. However, as described in the text, the interaction between case and violence only bordered significance (*P*=0.064). Future studies, possibly with a longitudinal design, will need to explore further the possibility that environmental violence might be related to brain changes in psychosis.

**Table S1.**

**Characteristics of the cohorts included**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SITE** | **Inclusion criteria for patients** | **Instrument/Diagnostic criteria** | **Measure of Violence** | **Measure of Income** | **Measure of Urbanicity** | **Scanner and Field Strength** | **Sequence used** voxel size(mm3), TI (ms) / TE (ms) / TR (ms) /Flip angle (°). |
| **Argentina - Buenos Aires** | Outpatients aged between 18-50 years old with a diagnosis of schizophrenia, stable on the same medication for at least two weeks. | CIDI / DSM-IV-TR / ICD-10 (F20) | Average homicide rates in neighborhood between 2011-2016 (http://www.consejomagistratura.gov.ar/instituto/main.html and https://estadisticascriminales.minseg.gob.ar). | Imputed from addresses between 2011-2016 (https://www.estadisticaciudad.gob.ar/eyc/?cat=84 and https://www.indec.gob.ar/informesdeprensa\_anteriores.asp?id\_tema\_1=4&id\_tema\_2=31&id\_tema\_3=60). | Neighborhood inhabitants in 2010 per km2 based on CNPHyV 2010 – INDEC (https://www.indec.gob.ar/censos\_provinciales.asp?id\_tema\_1=2&id\_tema\_2=41&id\_tema\_3=135&p=02&d=000&t=3&s=6&c=2010). | General Electric 3T. | 3D T1 Fast SPGR-IR; voxel size 1x1x1.2mm; min. TI delay 600 / TE 2.988 / TR 7.256 / Flip angle 8°. |
| **Brazil – São Paulo** | Outpatients aged between 16 – 68 with diagnosis of Schizophrenia or Schizoaffective disorder | SCID / DSM-IV-TR | Average Homicide rate in neighborhood  (https://www.redesocialdecidades.org.br/dados-abertos). | Average neighborhood family income  (https://www.redesocialdecidades.org.br/dados-abertos). | City district inhabitants per km2 based on the 2010 Brazilian Census (https://www.prefeitura.sp.gov.br/cidade/secretarias/subprefeituras/subprefeituras/dados\_demograficos/index.php?p=12758) | Siemens Magnetom Sonata 1.5T | 3D T1 SPGR; voxel size: 1x1x1mm; TI: 1100; TE: 3.4; TR: 2000/ Flip Angle: 15° |
| **Brazil – Porto Alegre** | Outpatients diagnosed with schizophrenia, aged 18-50 years old, under treatment as usual that were stable for at least 6 months and could not be currently in a psychotic episode. | SCID / ICD-10 (F20) | Average homicide rates in neighborhoods between 2011-2014 (https://www.ssp.rs.gov.br/indicadores-criminais and http://especiais.zh.clicrbs.com.br/especiais/raio-x-da-violencia/) | Average neighborhood family income (http://portoalegreemanalise.procempa.com.br/ and https://censo2010.ibge.gov.br/) | Neighborhood inhabitants  (http://portoalegreemanalise.procempa.com.br/  and https://censo2010.ibge.gov.br/) | Philips Achieva 1.5T | 3D T1 MPRAGE; voxel size 1x1x1mm; TI 1000 / TE 4.0 / TR 8.7 / Flip angle = 8º. |
| **Chile - Santiago** | Inpatients aged between 15-25 years old admitted with a first-episode of non-affective psychosis. Patients were minimally medicated. | MINI / ICD-10 (F20 and F23.2). | Average homicide rates in neighborhoods between 2012-2016 (http://www.fnsp.gob.cl/estadisticas-delictuales-por-comuna/). | Average wages in the neighborhood based on the CASEN survey (http://observatorio.ministeriodesarrollosocial.gob.cl/casen-multidimensional/casen/casen\_2013.php). | Neighborhood inhabitants in 2015 per km2 (http://reportescomunales.bcn.cl/2015/index.php/Categor%C3%ADa:Comunas). | Philips Ingenia 3T. | 3D T1 TFE; voxel size 1.0mm3 isotropic; min. TI delay 965.2 / TE 3.5 / TR 7.7/ Flip angle 8°. |
| **Colombia - Medellin** | Outpatients with a diagnosis of schizophrenia, aged between 18 and 60 years old, education level between 5 and 16 years, no history of intellectual disability or traumatic brain injury. | Diagnostic Interview for Genetic Studies (DIGS) / DSM-IV-TR | Homicide rates in neighborhoods in 2014 (https://www.medellincomovamos.org/presentaci-n-informe-de-calidad-de-vida-de-medell-n-2014-2015/) | Per capita income per spending unit in neighborhood in 2014  (https://www.medellin.gov.co/irj/go/km/docs/pccdesign/SubportaldelCiudadano\_2/PlandeDesarrollo/ObservatoriodePolticasPblicas/Shared%20Content/Pobreza%20en%20la%20ciudad%20de%20Medell%C3%ADn%2C%202014.pdf). | Neighborhood inhabitants per km2 in 2014 (Inhabitants: https://www.medellin.gov.co/irj/go/km/docs/wpccontent/Sites/Subportal%20del%20Ciudadano/Planeaci%C3%B3n%20Municipal/Secciones/Indicadores%20y%20Estad%C3%ADsticas/Documentos/Proyecciones%20de%20poblaci%C3%B3n%202005%20-%202015/02%20Proyecciones%20Poblaci%C3%B3n%20Medell%C3%ADn%202005-2015%20por%20comuna%20y%20correg.pdf  Area of each comuna: https://www.medellin.gov.co/irj/portal/medellin?NavigationTarget=navurl://06bdb4d911e35cb9d3de717115deedc3) | Philips Ingenia 3T. | 3D T1 TFE; voxel size 1.0mm3isotropic; TI delay 513.1 / TE 2.1 / TR 4.7 / Flip angle 8°. |
| **Mexico – Mexico City A** | Inpatient and outpatients aged between 13-47 years old, recruited during a first-episode of non-affective psychosis. All patients were antipsychotic-naïve. | Structured  clinical interview for DSM-IV | Average homicide rates in each municipality between 2013-2016 (http://onc.org.mx/estadistica-nacional/) | Monthly income of the family was obtained from hospital records and adjusted to inflation rates (http://www.anterior.banxico.org.mx/portal-inflacion/inflacion.html) | Inhabitants in each municipality per km2 in 2015 (https://www.inegi.org.mx/app/buscador/default.html?q=densidad+poblacion#tabMCcollapse-Indicadores) | GE Signa HDxt 3T. | 3D SPGR; voxel size 0.47x0.47x1.2mm3; TI 450 / TE 5.6 / TR 13 / Flip angle 20°. |
| **Mexico City B** | GE Signa HDxt 3T. | 3D FSPGR; voxel size 1.0mm3 isotropic; TI 450 / TE 5.0 / TR 12 / Flip angle 20°. |