Supplementary Material

Sample

Pelotas currently has 328,000 urban inhabitants and is located at the extreme South of Brazil, near the Uruguayan border, a region with higher degrees of European genetic contributions when compared to other parts of Brazil. Its main economic activities are rice production, commerce and education. At the time of the beginning of the study, the infant mortality rate was 21 deaths per thousand births. In Pelotas, a population-based birth cohort study was started in 1993, and subjects have been followed up at several points in time during infancy, childhood, adolescence and young adulthood. The original goals of the 1993 Cohort were to evaluate trends in maternal and child health indicators, through a comparison with results of the 1982 study; to assess associations between early life variables and later outcomes, with particular emphasis on the detection of critical windows; and to improve data quality, using the lessons learned from the 1982 study.(S1) Regarding ancestry, within a country of continental size like Brazil, population composition varies widely among regions. In Brazil as a whole, the population is highly admixed, but the southern Brazilian population differs from this general pattern as has been shown by admixture quantification studies.(S2,S3) This heterogeneity was documented in several genetic studies, using either uniparental or autosomal markers, which demonstrated a typical although non-uniform triethnic (European+African+Amerindian) pattern for the Brazilian population gene pool. Southern populations presented lower levels of African and higher degrees of European contributions when compared to other Brazilian groups. The assessment of the potential influence of our sample's ethnic admixture on regression analysis findings, including gender and "skin-color" as the only covariates to the initial model (5-HTTLPR, maltreatment, and their interaction), showed the small and non-significant impact of the variable skin color on our final model results, as shown in Table S4.

Multiplicative vs. additive model analyses

In keeping with our primary objective of replication of previous findings, our analysis followed the multiplicative model adopted by Caspi et al. in 2003, and further corroborated the existence of an interaction. However, using an additive model to assess the existence of an interaction, it also indicates the presence of this phenomenon in our sample. Following the strategy proposed by Knol et al.,(S4) we were able to identify an interaction using a model that investigates departure from additivity by estimating the relative excess risk due to interaction (RERI), the proportion of disease among those with both exposures that is attributable to their interaction (AP) and the ratio between the combined effect and the sum of the individual effects, the synergy index (S). In our analysis, the values for these indicators were a RERI of 0.31, an AP of 0.207 and an S of 2.63. We therefore identified evidence of GxE on both multiplicative and additive scales in our sample.

TABLE S1. Sample characteristics for individuals evaluated at the last wave of the 1993 Pelotas cohort (18/19 years) and for those lost on follow-up (retention rate of 81.3%).

	Non-retained	Retained	Total*
Male	51.5%[a]	49.1%[a]	49.6%
White skin color	69.7%[a]	66.5%[a]	66.8%
Maternal education (years)			
0 - 4	20.3%[a]	24.9%[b]	24.4%
5 - 8	45.8%[a]	48.0%[a]	47.8%
9 or more	34.0%[a]	27.1%[b]	27.8%
Family income (minimum wages)	4.20 (5.98)	4.21 (5.63)	4.20 (5.67)
Maternal psychopathology	32.1%[a]	30.8%[a]	30.9%
Total	982	4,267	5,249

* Presented percentages and mean values refer to available data. Categorical variables presented as percentages (according to column); continuous as mean (standard deviation). Compared to those lost on follow-up, the retained sample showed similar rates of male gender, white-skin color and maternal psychopathology, as well as mean family income. There were differences regarding maternal education, as shown in Table S1 (p=0.003). Superscript letters denote column proportions differences: different letters show significant and equal letters indicate non-significant differences from each other at a 0.05 level.

TABLE S2. Sample characteristics for individuals included and excluded from final analysis.

	Included	Excluded	Total**
Male	45.7%[a]	50.7%[b]	47.4%
White skin color	69.7%[a]	59.9%[b]	66.6%
Maternal education (years)			
0 - 4	28.7%[a]	17.8%[b]	25.2%
5 - 8	47.5%[a]	50.0%[a]	47.6%
9 or more	23.8%[a]	32.3%[b]	26.6%
Family income (minimum wages)	4.57 (6.05)[a]	3.48 (4.40)[b]	4.22 (5.59)
Maternal psychopathology	23.2%[a]	47.9%[b]	30.5%
5-HTTLPR genotype			
SS	19.8%	18.0%	19.2%
LS	47.8%	48.9%	48.4%
LL	32.4%	33.1%	32.4%
Childhood maltreatment			
No	70.8%[a]	57.8%[b]	66.8%
Probable	17.7%[a]	20.3%[a]	18.6%
Severe	11.5%[a]	21.8%[b]	14.6%
Depressive episode			
Yes	3.3%[a]	5.5%[b]	4.0%
Total*	2,392	1,039	3,558

*The sum of included and excluded samples differs from the total number shown due to 127 individuals with non-available data for early depressive symptoms screening evaluation. **The proportions in this column differ from the retained column in Table S1 since here only individuals with all data required for the primary analysis are presented. Categorical variables presented as percentages (according to column); continuous as mean (standard deviation). Results derived from chi-square ($\chi 2$) test for categorical and t-test to compare the groups' mean for quantitative variables. Superscript letters denote column differences: different letters show significant and equal letters indicate non-significant differences from each other at a 0.05 level.

TABLE S3: Questions on childhood maltreatment, asked confidentially at the 2008 assessment, freely and unofficially translated from Brazilian Portuguese to English language.

1. Have you ever been separated from your parents to be cared for by someone else?

2. Have you had, in your home, fights with physical aggression between adults or an adult who assaulted a child or teenager?

3. Has it happened of not having enough food at home or wear dirty or torn clothes because you had no other?

4. Have you ever thought or felt that your parents whished you were never born?

5. Have you ever thought or felt that someone in your family hated you?

6. Did it ever an adult in your family or someone who was taking care of you beat you in a way that has hurt you or left you with marks?

7. Did it ever someone tried to touch you in a sexual way, or tried to make you touch them against your will, threatening you or hurting you?

TABLE S4. Regression analysis results for gene and environment interaction (GxE) assessment including gender and skin color as the only covariates to the model.

	B	SE	p-value
Childhood Maltreatment	0.47	0.21	0.03
5-HTTPLR Genotype	-0.52	0.25	0.04
GxE	0.46	0.19	0.01
Gender	0.60	0.26	0.02
Skin Color	0.15	0.24	0.55

Reference category for gender: male. Reference category for skin color: white skin color. 5-HTTLPR: Serotonin transporter linked polymorphic region. B: Regression coefficient. SE: Standard Error.

References

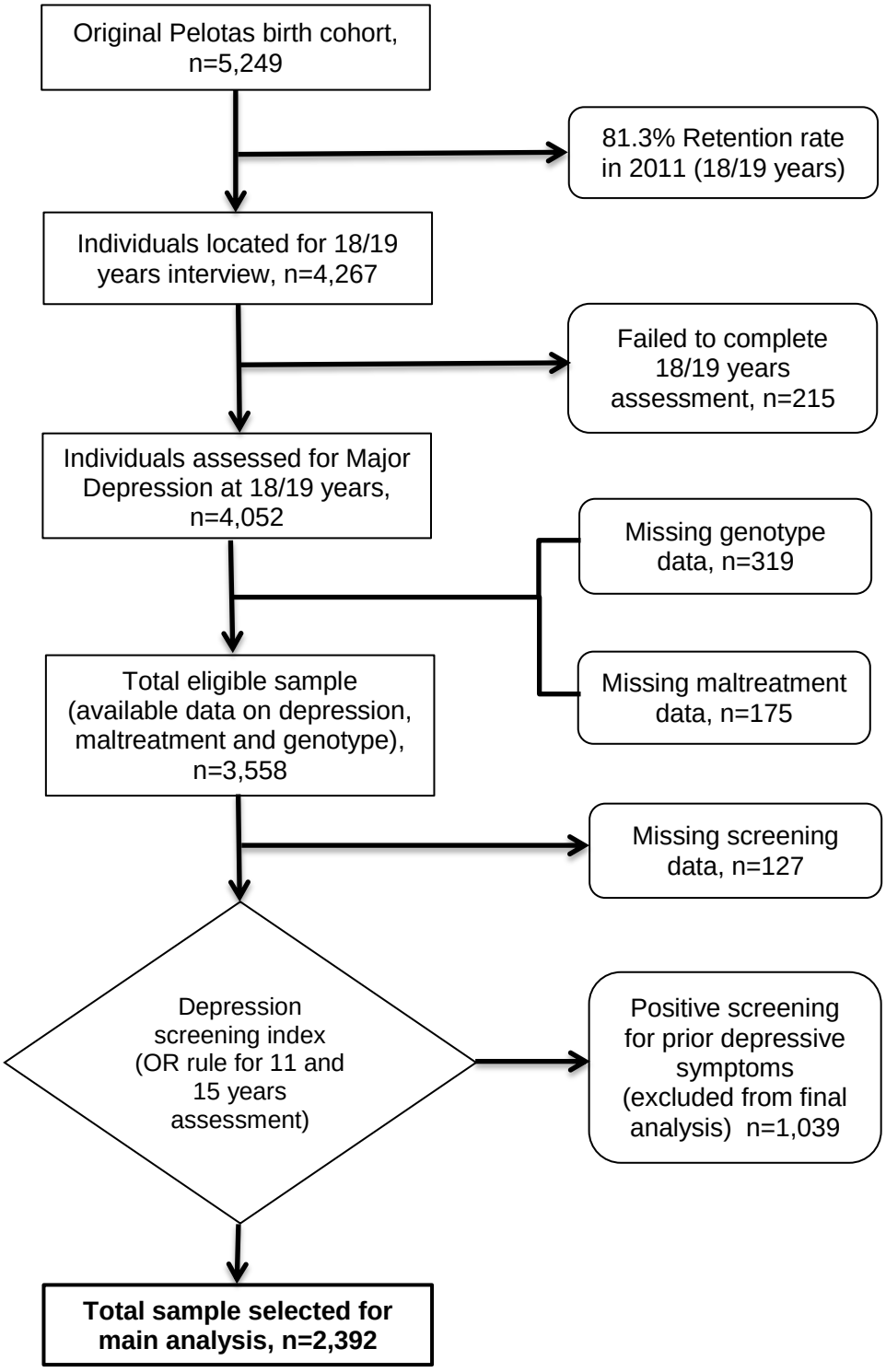
S1. Victora CG, Araújo CL, Menezes AM, Hallal PC, Vieira MeF, Neutzling MB, et al. Methodological aspects of the 1993 Pelotas (Brazil) Birth Cohort Study. Rev Saude Publica. 2006;40(1):39-46.

S2. Salzano FM, Bortolini MC (2002) The evolution and genetics of Latin American populations. Cambridge University Press, Cambridge.

S3. Callegari-Jacques SM, Grattapaglia D, Salzano FM, Salamoni SP, Crossetti SG, Ferreira ME, Hutz MH (2003) Historical genetics: spatiotemporal analysis of the formation of the Brazilian population. Am J Hum Biol 15:824-834.

S4. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol. 2007;36(5):1111-8.

FIGURE S1. Study design flowchart



Depression screening index combines scores from all available emotional and impact SDQ scale. As recommended for the Brazilian Portuguese version of the original instrument, self-assessment emotional SDQ scores equal or over 6 and parent assessment equal or over 4 were considered a positive emotional problems screening if each were also accompanied by impact SDQ evaluation scores equal or over 1. Any positive emotional problems screening was considered compatible to positive depression screening index (OR approach).