**Supplementary Information**

### **1. Prenatal adversity sum score**

The clinical cut-offs used in our study have been established in a Finnish sample, by using the first 500 participant mothers’ questionnaire data of the FinnBrain Birth Cohort Study (Karlsson et al., 2018). In our child behavior sample, the 85th percentiles of the respective questionnaire were as follows: EPDS (t1/t2/t3= 9), SCL (t1= 6, t2= 8, t3= 6) and PRAQ-R (t2/t3= 29). Thereby, in our sample, the 85th percentiles of the EPDS questionnaire and the SCL anxiety subscale were low compared to most recommended clinical cutoffs (e.g., Levis et al., 2020; Lyubenova et al., 2021; Pedersen & Karterud, 2004). Using the 85th percentiles for EPDS, SCL anxiety and PRAQ-R2 for determining PRE-AS, results were very similar to those obtained with the clinical cut-offs, with following exceptions: The GxE interaction on F4 at 5 years was no longer significant with the continuous SDQ F4 values, but was significant with the dichotomized SDQ F4 values, and the GxExSex interaction effect on F2 at 4 years became significant. *Post hoc* analyses, performed separately in boys and girls, revealed that the GxE interaction on F2 at 4 years was insignificant in both boys (beta: 0.08, SE: 0.05, p= 0.128) and girls (beta: -0.09, SE: 0.06, p= 0.121).

### **2. Statistical analyses**

Assumptions of the multiple regression analyses were checked by visual inspection of the correct specification of the model (Residuals vs Fitted plot, Lowess line), the normal distribution of the residuals (Normal Q-Q plot), the homoscedasticity (Scale-Location diagram) and critical outliers (Residuals vs. Leverage plot, Cook’s distance) (‘plot’ function in R). Assumptions were met in all analyses unless otherwise stated. Homoscedasticity was additionally tested by means of the Goldfeld-Quandt-test (‘gqtest’ function in R); a p-value > 0.05 indicates homoscedasticity. Heteroscedasticity was observed in analyses with SDQ F1 values at 4 years and SDQ F4 values at 5 years. In case of non-normally distributed residuals and heteroscedasticity, we additionally computed a factor with two levels, representing two extreme groups of the respective variable (≤20%, ≥80%), and used this variable in binomial regression analyses as dependent variable. This resulted in additional control analyses for SDQ F1 and F4 at both 4 years and 5 years.

Furthermore, we reran the main analyses in control analyses excluding a) mothers with CNS affecting medication (including antidepressants), prenatal alcohol and/or illicit drug intake, and b) offspring with Apgar scores <5, asphyxia and/or birth weight <1500g. These control variables constitute potential or established risk factors. For instance, while studies on the effects of psychotropic medication on early child development have yielded mixed results (El Marroun et al., 2014; Field, 2017), recent studies reported sex-specific variations of white matter structure in SSRI-exposed infants (e.g., Campbell et al., 2021) and animal studies suggest age- and sex-specific altered hippocampal synaptic plasticity in perinatally SSRI-exposed animals (Pawluski & Gemmel, 2018).

Packages in use were “psych” (Revelle, 2018) and “missForest” (Stekhoven, 2013) among others.

**3. Results**

**3.1 Demographic overview**

With regard to the subscales of PRE-AS, several measures differed significantly between the child behavior sample and the neuroimaging sample such as SCL-pre, EPDS-pre, RDAS-pre and PRAQ being significantly higher and maternal prenatal physical diseases significantly lower in the neuroimaging sample. POST-DS was higher in the neuroimaging sample compared to the child behavior sample. In addition, in the child behavior sample, significant sex differences were found for postnatal SCL (p= 0.016) and gestational weeks ≤37 (p= 0.033) revealing higher risk in mothers of boys than in those of girls. In the neuroimaging sample, lower Apgar scores were observed for boys compared to girls (p=0.015).

**3.2 Association of PRE-AS with child problem behavior**

In our control analyses, excluding mothers with CNS affecting medication, alcohol and/or illicit drug intake, all significant associations between PRE-AS and SDQ scores remained significant (N= 1109). Excluding children with low Apgar scores, asphyxia and/or low birth weight, all significant associations between PRE-AS and SDQ scores remained significant, and additionally significantly higher conduct problems (SDQ F2 scores) at 5 years were observed in boys compared to girls (N= 1397).

**3.3 Association of PRE-AS with infant amygdalar and hippocampal volumes**

In the control analyses, excluding infants with low Apgar scores and/or asphyxia (resulting sample N= 107), the sex-specific association with right amygdalar volumes stayed significant (p= 0.031), but was reduced to non-significance (trend-level significance) for left amygdalar volumes (p= 0.096). Post hoc statistical analyses with the control variables as covariates suggest that the reduction to non-significance is due to the reduction in sample size (left amygdala: p= 0.017).

Excluding mothers with medication, alcohol and/or illicit drug intake (resulting sample N= 81), the interaction of PRE-AS with sex on both right (p= 0.134) and left amygdalar volumes (p= 0.231) was reduced to non-significance. Post hoc statistical analyses with the control variables as covariates suggest that the reduction to non-significance is due to the reduction in sample size (right amygdala: p= 0.029, left amygdala: p= 0.026).

**3.4 ePRS – by – environment interaction effects on SDQ**

The ePRS-by-PRE-AS interaction effect stayed significant after controlling for POST-DS, in the analysis with the dichotomous SDQ F4 factor as a dependent variable and in the control analysis excluding mothers with CNS affecting medication, alcohol and drug intake (resulting sample N= 823), but was reduced to non-significance by correcting for multiple comparisons and in the control analysis excluding children with asphyxia, apgar <5 or birthweight < 1500g (resulting sample N= 1046, p= 0.196). The post hoc statistical analysis with the control variables as covariates yielded significant results (p= 0.030).

Additional exploratory *post hoc* analyses with the PRE-POST factor showed that, in the subgroup with low genetic risk, SDQ F4 values were significantly higher in children with both pre- and postnatal adversity (>0/>0) compared to children with no pre- and postnatal adversity (0/0) (β±SE: 0.68±0.15, p< 0.001). SDQ F4 values were also non-significantly higher in children with only prenatal adversity (β±SE: 0.24±0.17, p= 0.155), while no effects were observed in children with only postnatal adversity (β±SE: 0.03±0.23, p= 0.901). No significant associations with PRE-POST were observed in the subgroup with high genetic risk (all p > 0.12), and effects were comparably weak in children with either pre- or postnatal adversity (PRE-AS > 0: β±SE: 0.17±0.20, p= 0.408; POST-DS > 0: β±SE: 0.18±0.25, p= 0.480).

**3.5 ePRS – by – environment interaction effects on amygdalar and hippocampal volumes**

The GxExSex interaction effect on right hippocampal volumes stayed significant after including the control variable POST-DS (with and without correction for multiple comparisons), and after excluding mothers with CNS affecting medication and/or alcohol/illicit drug intake, but was reduced to non-significance in the subsample of infants with no asphyxia nor low Apgar scores (p= 0.302). in the latter subsample, significant GxE interaction effects on right (β±SE: 15.63±7.27, p= 0.035) and left hippocampal volumes (β±SE: 18.79±7.42, p= 0.013) emerged, independent of sex. Of note, in this subsample, the number of female infants was lower than that of male infants [girls: n= 37 (41.1%), boys: n= 53]. The *post hoc* statistical analysis with the control variables as covariates yielded significant results (p= 0.001).

**Table SI-1:** Descriptive information for the child behavior and the neuroimaging samples. Mean values (M) with standard deviations (SD) and ranges, or the frequencies are given. In the right column, the p-values of the differences between the samples (boys and girls combined), assessed with t-tests or chi-squared tests, are presented.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Child behavior sample (n= 1568) | | | Neuroimaging sample (n=122) | | | | Δ  Sample | |
| M±SD (range); frequency (no/yes) | Whole sample | Boys | Girls | | Whole sample | Boys | Girls | | p-value |
| PRE-AS | 1.53±1.43  (0-9) | 1.58±1.46 (0-9) | 1.47±1.40 (0-7) | | 1.71±1.72 (0-7) | 1.71±1.68  (0-6) | 1.72±1.79  (0-7) | | 0.185 |
| SCL-pre | 1354/214  (*mis:* 147) | 733/125  (*mis: 84*) | 621/89  (*mis: 63*) | | 93/29  (*mis: 3*) | 53/16  (*mis: 2*) | 40/13  (*mis: 1*) | | 0.002 |
| PRAQ | 1425/143  (*mis:* 114) | 781/77  (*mis: 67*) | 644/66  (*mis: 47*) | | 99/23  (*mis: 4*) | 55/14  (*mis: 3*) | 44/9  (*mis: 1*) | | <0.001 |
| EPDS-pre | 1351/217  (*mis:* 139) | 736/122  (*mis: 85*) | 615/95  (*mis: 54*) | | 94/28  (*mis: 3*) | 53/16  (*mis: 2*) | 41/12  (*mis: 1*) | | 0.006 |
| Lack of money | 1321/247  (*mis:* 235\*) | 720/138  (*mis: 134\**) | 601/109  (*mis: 101*) | | 96/26  (*mis: 13*) | 54/15  (*mis: 9*) | 42/11  (*mis: 4)* | | 0.108 |
| Low education | 1305/263  (*mis:* 54) | 710/148  (*mis:* 31) | 595/115  (*mis: 23*) | | 105/17  (*mis: 1*) | 59/10  (*mis: 1*) | 46/7 | | 0.417 |
| Violence | 1535/33  (*mis:* 160) | 840/18  (*mis: 88*) | 695/15  (*mis: 72*) | | 121/1  (*mis: 12*) | 69/0  (*mis: 7*) | 52/1  (*mis: 5*) | | 0.330 |
| RDAS-pre | 1248/320  (*mis:* 103) | 683/175  (*mis: 61*) | 565/145  (*mis: 42*) | | 86/36  (*mis: 6*) | 49/20  (*mis: 3*) | 37/16  (*mis: 3*) | | 0.018 |
| Smoking | 1404/164  (*mis:* 139) | 765/93  (*mis: 8*0) | 639/71  (*mis: 59*) | | 113/9  (*mis: 8)* | 64/5  (*mis: 4*) | 49/4  (*mis: 4*) | | 0.279 |
| Prenatal physical disease | 920/648  (*mis:* 56) | 489/369  (*mis:* 30) | 431/279  (*mis: 26*) | | 84/38  (*mis: 2*) | 47/22  (*mis: 1*) | 37/16  (*mis: 1*) | | 0.027 |
| Birth size low/high | 1490/78  (*mis:* 22) | 814/44  (*mis: 8*) | 676/34  (*mis: 14*) | | 121/1  (*mis: 2*) | 69/0  (*mis: 1*) | 52/1  (*mis: 1*) | | 0.036 |
| GWK ≤37 | 1493/75 | 808/50 | 685/25 | | 121/1 | 69/0 | 52/1 | | 0.042 |
| Birth weight [g] | 3552±513  (940-5470)  *(mis: 21)* | 3596±541 (940-5470)  *(mis: 7)* | 3500±472  (1410-4975)  *(mis: 14)* | | 3484±430  (2530-4700)  *(mis: 1)* | 3565±452  (2720-4700) | 3379±380 (2530-4340)  *(mis: 1)* | | 0.155 |
| Apgar 5 min | 9.06±0.80  (3-10)  *(mis: 27)* | 9.06±0.77 (3-10)  *(mis: 12)* | 9.06±0.84  (3-10)  *(mis: 15)* | | 8.98±0.90  (4-10) *(mis: 1)* | 8.81±1.08 (4-10) | 9.21±0.53 (8-10)  *(mis: 1)* | | 0.348 |
| POST-DS | 1.65±1.89  (0-10) | 1.71±1.94 (0-10) | 1.57±1.81 (0-9) | | 2.10±2.45 (0-10) | 2.26±2.52  (0-10) | 1.89±2.37  (0-9) | | 0.013 |
| SCL-post | 0.21±0.59  (0-3)  (*mis:* 743\*) | 0.25±0.64 (0-3)  (*mis:* 400\*) | 0.18±0.52 (0-3)  (*mis:* 343\*) | | 0.35±0.86 (0-3)  (*mis:* 75) | 0.42±0.93 (0-3)  (*mis: 47*) | 0.26±0.76  (0-3)  (*mis: 28*) | | 0.017 |
| EPDS-post | 0.24±0.58  (0-3)  (*mis:* 796\*) | 0.25±0.61 (0-3)  (*mis:* 429\*) | 0.22±0.53 (0-3)  (*mis:* 367\*) | | 0.35±0.73 (0-3)  (*mis:* 78) | 0.41±0.73  (0-3)  (*mis: 49*) | 0.28±0.72  (0-3)  (*mis: 29*) | | 0.035 |
| RDAS-post | 1.03±1.25  (0-3)  (*mis:* 836\*) | 1.04±1.25 (0-3)  (*mis:* 451\*) | 1.02±1.25 (0-3)  (*mis:* 385\*) | | 1.25±1.33 (0-3)  (*mis:* 83) | 1.29±1.35  (0-3)  (*mis: 53*) | 1.21±1.32  (0-3)  (*mis: 30)* | | 0.054 |
| Mother’s age at birth | 30.9±4.4  (18-45) | 30.9±4.3  (19-44) | 31.0±4.4 (18-45) | | 29.8±4.4 (19-41) | 30.0±4.58  (19-41) | 29.4±4.3  (21-41) | | 0.004 |
| Maternal medication (CNS affecting) | 1496/72  (*mis:* 153) | 819/39  (*mis:* 89) | 677/33  (*mis:* 64) | | 110/12  (*mis:* 6) | 61/8  (*mis: 3*) | 49/4  (*mis: 3*) | | 0.010 |
| Maternal alcohol and/or illicit drug consumption | 1166/402  (*mis:* 137) | 626/232  (*mis:* 79) | 540/170  (*mis:* 58) | | 92/30  (*mis:* 9) | 48/21  (*mis: 5*) | 44/9  (*mis: 4*) | | 0.798 |
| Infant asphyxia | 1425/143  (*mis:* 22) | 775/83  (*mis:* 8) | 650/60  (*mis:* 14) | | 109/13  (*mis:* 2) | 63/6  (*mis:* 1) | 46/7  (*mis:* 1) | | 0.572 |

\* missing value of at least one time point, PRE-AS= prenatal adversity sum score, POST-DS= postnatal distress sum score, pre= prenatal, post= postnatal, SCL= anxiety symptoms, EPDS= depressive symptoms, PRAQ= pregnancy-related anxiety

**Table SI-2: Association between PRE-AS and SDQ - nonimputed data.** Results that are no longer significant compared with the imputed data (Table 2) are marked blue.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | M±SD  (range, N) | | | | Association with PRE-AS | | | Sex-specific association with PRE-AS | |
|  | Whole sample  (range, N) | Boys  (range, N) | Girls  (range, N) | β-values ± SE | | p | β-values ± SE | | P |
| 4 years | | | | | | | | | |
| SDQ F1 | 1.06±1.19  (0-9, 861) | 1.03±1.21  (0-9, 470) | 1.10±1.17  (0-6, 391) | 0.097±0.029 | | <0.001 | 0.145±0.058 | | 0.012 |
| SDQ F2 | 2.99±1.87  (0-9, 861) | 3.12±1.92  (0-9, 470) | 2.84±1.80  (0-8, 391) | 0.188±0.045 | | <0.001 | 0.133±0.090 | | 0.140 |
| SDQ F3 | 3.06±2.11  (0-10, 861) | 3.45±2.15  (0-10, 470) | 2.58±1.96  (0-9, 391) | 0.263±0.049 | | <0.001 | 0.013±0.099 | | 0.896 |
| SDQ F4 | 1.83±1.51  (0-9, 861) | 2.00±1.66  (0-9, 470) | 1.63±1.28  (0-7, 391) | 0.079±0.036 | | 0.029 | 0.174±0.073 | | 0.017 |
| SDQ Sum | 8.95±4.45  (0-26, 861) | 9.61±4.59  (1-26, 470) | 8.15±4.14  (0-22, 391) | 0.627±0.104 | | <0.001 | 0.465±0.209 | | 0.026 |
| 5 years | | | | | | | | | |
| SDQ F1 | 1.25±1.33  (0-8, 1049) | 1.24±1.37  (0-8, 574) | 1.26±1.29  (0-8, 475) | 0.206±0.030 | | <0.001 | 0.051±0.060 | | 0.395 |
| SDQ F2 | 2.81±1.96  (0-10, 1049) | 2.95±2.00  (0-10, 574) | 2.65±1.90  (0-8, 475) | 0.245±0.044 | | <0.001 | 0.079±0.088 | | 0.368 |
| SDQ F3 | 3.14±2.32  (0-10, 1048) | 3.49±2.34  (0-10, 573) | 2.72±2.23  (0-10, 475) | 0.379±0.050 | | <0.001 | -0.055±0.102 | | 0.591 |
| SDQ F4 | 1.57±1.50  (0-9, 1048) | 1.72±1.69  (0-9, 573) | 1.39±1.20  (0-6, 475) | 0.179±0.033 | | <0.001 | 0.139±0.067 | | 0.039 |
| SDQ Sum | 8.77±4.84  (0-27, 1048) | 9.39±5.05  (0-27, 573) | 8.02±4.46  (0-25, 475) | 1.009±0.104 | | <0.001 | 0.214±0.210 | | 0.309 |

**Table SI-3:** **PRE-AS and amygdalar / hippocampal volumes - nonimputed data.** Results are similar compared to Table 3.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Volumes [mm^3]  M±SD | | | | Association with  PRE-AS | | | Sex-specific association with PRE-AS | |
|  | Whole sample  (N= 98) | Boys  (N= 55) | Girls  (N= 43) | β-values ± SE | | p | β- values ± SE | | P |
| R Amy | 265±39 | 275±39 | 252±35 | 0.04±2.02 | | 0.983 | -8.82±3.92 | | 0.027 |
| L Amy | 268±37 | 273±41 | 262±31 | -1.44±1.89 | | 0.450 | -8.80±3.66 | | 0.018 |
| R Hippoc | 771±106 | 783±103 | 755±109 | -5.62±5.16 | | 0.279 | 4.83±10.28 | | 0.640 |
| L Hippoc | 768±116 | 789±119 | 742±109 | -7.64±5.86 | | 0.195 | 14.04±11.58 | | 0.228 |

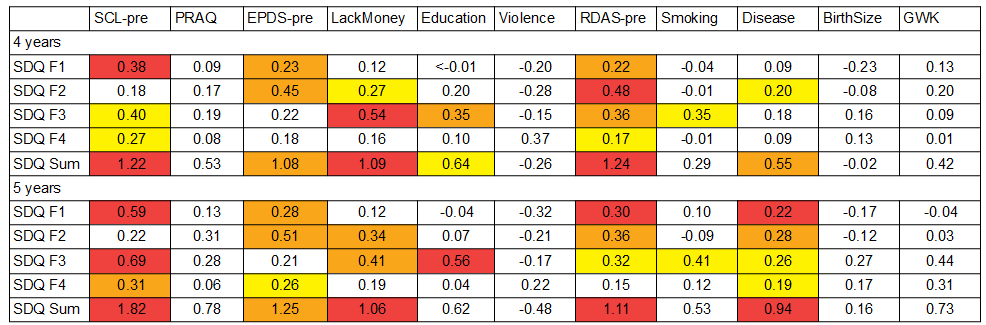
**Table SI-4: Genotype, SDQ and PRE-AS** **– nonimputed data.** Results that are significant with the raw, but not with the imputed data (Table 4) are marked red. Results that are no longer significant compared with the imputed data (Table 4) are marked blue.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Association with ePRS | | | Sex-specific association with ePRS | | | Association of the GxE interaction  (ePRS by PRE-AS) | | | Association of the sex-specific GxE interaction (ePRS by PRE-AS by sex) | |
|  | β-values ± SE | p | β-values ± SE | | p | β-values ± SE | | p | β-values ± SE | | p |
| 4 years | | | | | | | | | | | |
| SDQ F1 | -0.02±0.05  (N= 817) | 0.608 | 0.06±0.09 | | 0.541 | -0.03±0.04  (N= 642) | | 0.415 | 0.05±0.07 | | 0.480 |
| SDQ F2 | 0.03±0.07  (N= 817) | 0.691 | -0.21±0.14 | | 0.119 | 0.03±0.05  (N= 642) | | 0.622 | 0.04±0.11 | | 0.728 |
| SDQ F3 | 0.09±0.07  (N= 817) | 0.214 | -0.32±0.15 | | 0.032 | -0.01±0.06  (N= 642) | | 0.931 | -0.11±0.12 | | 0.374 |
| SDQ F4 | -0.02±0.05  (N= 817) | 0.683 | 0.06±0.11 | | 0.543 | -0.02±0.04  (N= 642) | | 0.674 | 0.10±0.09 | | 0.264 |
| SDQ Sum | 0.08±0.16  (N= 817) | 0.646 | -0.41±0.33 | | 0.207 | -0.03±0.12  (N= 642) | | 0.837 | 0.08± 0.25 | | 0.749 |
| 5 years | | | | | | | | | | | |
| SDQ F1 | <-0.01±0.04  (N= 1032) | 0.993 | 0.10±0.09 | | 0.247 | <-0.01±0.03  (N= 803) | | 0.911 | 0.07±0.07 | | 0.302 |
| SDQ F2 | 0.08±0.06  (N= 1032) | 0.183 | -0.08±0.12 | | 0.540 | 0.01±0.05  (N= 803) | | 0.909 | -0.16±0.11 | | 0.133 |
| SDQ F3 | 0.07±0.07  (N= 1031) | 0.362 | -0.12±0.14 | | 0.405 | 0.03±0.06  (N= 802) | | 0.662 | -0.12±0.12 | | 0.338 |
| SDQ F4 | 0.05±0.05  (N= 1031) | 0.329 | -0.02±0.09 | | 0.797 | -0.06±0.04  (N= 802) | | 0.113 | 0.11±0.08 | | 0.157 |
| SDQ Sum | 0.19±0.15  (N= 1031) | 0.209 | -0.12±0.31 | | 0.697 | -0.03±0.12  (N= 802) | | 0.788 | -0.09±0.25 | | 0.717 |

**Table SI-5: Genotype, amygdalar / hippocampal volumes and PRE-AS** – **nonimputed data.** Results are similar compared to Table 5.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Association with ePRS  (N=106) | | | Sex-specific association with ePRS (N=106) | | | Association of the GxE interaction  (ePRS by PRE-AS,  N=83) | | Association of the sex-specific GxE interaction (ePRS by PRE-AS by sex, N=83) | |
|  | β-values ± SE | p | β-values ± SE | | p | β-values ± SE | | p | β-values ± SE | P |
| R Amy | 4.99±3.45 | 0.151 | 10.43±7.63 | | 0.175 | -0.67±2.19 | | 0.762 | -0.40±4.32 | 0.927 |
| L Amy | 1.89±3.34 | 0.573 | -1.61±7.45 | | 0.829 | 1.68±2.03 | | 0.410 | 3.68±4.08 | 0.369 |
| R Hippoc | 3.88±9.55 | 0.685 | -3.63±21.33 | | 0.865 | 1.94±5.60 | | 0.731 | 35.78±10.86 | 0.002 |
| L Hippoc | 8.27±10.06 | 0.413 | 12.13±22.44 | | 0.590 | 3.91±6.21 | | 0.531 | 18.77±12.66 | 0.143 |

**Table SI-6: The associations of the single risk factors with child emotional and behavioral outcome.** The associations were assessed as regression estimates in multiple regression analyses. Beta values are shown. P-values: red <0.001, orange <0.01, yellow <0.05.



**Figure SI-1: SDQ scores and pre- and postnatal adversity.** SDQ scores (mean values and their confidence intervals) are depicted for children, split into four groups: 1) PRE-AS=0 and POST-DS=0 (0/0), 2) PRE-AS>0 and POST-DS=0 (>0/0), 3) PRE-AS=0 and POST-DS>0 (0/>0), and 4) PRE-AS>0 and POST-DS>0 (>0/>0). Significant differences were found for most of the comparisons with group 4. Significant differences comparing PRE-AS=0 versus PRE-AS>0 under the condition of no postnatal distress were observed for SDQ F3 and SDQ Sum scores at 4 and 5 years and SDQ F2 scores at 5 years. No significances are reported for the group 0/>0.

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**Figure SI-2:** A three-dimensional scatterplot of the distribution of PRE-AS scores, right amygdalar volumes and SDQ F3 scores in 4-year old girls (N=38)



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