**SUPPLEMENTARY INFORMATION (SI)**

**sMethods**

**Polygenic scores (PGSs)**

The genome-wide genotyping in ELSA was performed at University College London Genomics in 2013-2014 using the Illumina HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3). All non-European ethnic groups - genetically established and self-reported - were excluded from the sample. Using PLINK1, R2 and VCFtools3, single-nucleotide polymorphism (SNPs) were excluded if they were non-autosomal, the minor allele frequency was <0.01%, if more than 2% of genotype data were missing, and if the Hardy-Weinberg Equilibrium *P*-value was <10−4. Samples were removed based on call rate (<0.99), suspected non-European ancestry, sex difference in allelic frequency of ≥0.2, heterozygosity and relatedness. We employed principal components analysis4 to identify those individuals who deviated from the ethnic population they self-reported to be (i.e., ethnic outliers)4,5. This set of analyses demonstrated the presence of ancestral admixture in 65 individuals, who were subsequently removed. Concordant genetic ancestry and self-reported ethnicity participants were retained for further analyses. After these quality control steps, 7183 (96.9% n=7412) individuals and 1372240 (61.5% of n=2230767 SNPs) directly genotyped SNPs remained for further analyses.

To calculate PGSs for Major Depressive Disorder (MDD) and CRP, SNPs associated with each of these outcomes were weighted by their effect size derived from recent genome-wide meta-analyses of MDD and CRP respectively, and summed in a continuous score using PRSice.6 As previous research highlighted that PGSs built from directly genotyped data either had more predictive power7 or did not differ significantly from PGSs calculated using imputed data8, we calculated PGSs based on genotyped data at different *P*-value cut-offs. Because PGSs including all available SNPs either explain the most amount of variation in a trait or are not significantly different than PGSs based on different *P*-value thresholds8, we utilised a single *P*-value threshold of 1 for all PGSs. This enabled us to limit multiple testing while maximising the potential predictive ability of the PGSs.

**Covariates**

All covariates except medication use were measured in wave 3, concurrently to the assessment of ACEs. Medication use was measured only once in wave 6. Sex was a binary variable and age was measured in years. Childhood socioeconomic position was measured using data from the Life History interview on overcrowding (number of people/number of bedrooms > 1), number of books in the home (none vs one or more), father’s occupation (manual vs other), financial hardship, and parent unemployment. Based on these measures, we calculated a cumulative score representing the total number of childhood socioeconomic adversities reported by the participant. Anti-inflammatory and antihypertensive medications were grouped into a single binary variable (yes/no). Use of antidepressants was also treated as a binary variable (yes/no). For descriptive purposes only, we also measured adult wealth and educational attainment. Adult wealth was derived from a comprehensive assessment of the participant’s economic resources (e.g. financial, housing and physical wealth) excluding pension wealth and was categorised into quintiles (1= lowest wealth; 5 = highest wealth). Educational attainment was indexed by a binary variable for whether the participant had a degree qualification or not.

**Latent growth mixture (LGM) modelling of depressive symptoms**

LGM models are characterised by the combination of latent growth curve modelling and latent class analysis. Such method allows to group individuals into trajectories according to their pattern of change.9 We estimated LGM models with a specific intercept and slope growth factor for each trajectory. The within-group variation for each trajectory is represented by the intercept and slope growth factors since they are modelled as continuous latent variables. The optimal number of trajectories was identified using a stepwise approach. First, we fitted one LGM model with a single trajectory. Second, we included an additional trajectory at each following step until the optimal number of trajectories was reached. The optimal number of trajectories was determined using the following criteria: lower sample-size adjusted Bayesian Information Criterion (ssaBIC); every class containing more than 5% of participants; and entropy value (i.e. quality of the classification model) closer to 1.10 In addition, we also evaluated the interpretability of the classes and whether they were theoretically meaningful for our research questions. The three-class solution was selected as the best fitting model since it had the best combination of lower AIC/ssaBIC and higher entropy, contained more than 5% of participants in each class, and had good interpretability.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **LGM model fit indices** | | | | |
|  | **2 classes** | **3 classes** | **4 classes** | **5 classes** |
| *AIC* | -39235.44 | **-38235.04** | -38110.06 | -38074.74 |
| *ssaBIC* | -39260.00 | **-38281.09** | -38048.66 | -37997.99 |
| *N classes >5%* | Yes | **Yes** | No | No |
| *Entropy* | 0.9995 | **0.9999** | 0.9999 | 0.9994 |

**Multiple imputation analysis**

Missing data on ACEs, outcome variables, and covariates were estimated using multiple imputation by chained equations (MI). All variables included in the analysis were used as predictors in the imputation models. We also used supplementary auxiliary variables including socioeconomic data, physical health, lifestyle factors, survey weights, and covariates from other waves of the study. The missing data were imputed under the missing at random (MAR) assumption. In our analysis, the MAR assumption implies that reliable estimates of the missing data can be computed if all the variables associated with the missing data generation process are included in the imputation model. Age and socioeconomic position are the main drivers of non-response and attrition in ELSA11. Therefore, as these variables were included in the imputation models, the MAR assumption is likely to be valid in our analysis. We created twenty imputed datasets. The estimates from LGM, multinomial, and logistic regression analyses were pooled used Rubin’s rules.12

**sRESULTS**

**Sensitivity Analyses**

1. *E-values*

The following ranges of E-values were calculated for the additive effects of ACEs and PGSs (imputed data analysis): Moderate depressive symptoms = 1.37–1.88; High depressive symptoms = 2.24–5.31 (sTable2); High CRP w4 = 1.18–1.52; High CRP w2-6 = 1.14–1.42 (sTable3). The E-values for moderate depressive symptoms and CRP were smaller than those for high depressive symptoms, suggesting that relatively modest unmeasured confounder effects could explain away their associations with the risk factors. However, the analysis did adjust for the most likely confounders of the association of ACEs with depression and CRP. In addition, the associations of the PGSs could only be confounded by different genetic variants than those included in the MDD and CRP PGSs, which should not play a major role in the aetiology of depression and chronic inflammation.

1. *Influence of antidepressants and CRP-related medications*

We estimated the associations presented in the main imputed data analysis without adjustment for antidepressants and CRP-related medications (i.e. anti-inflammatory or antihypertensive drugs) to understand the influence of these variables (sTable 5). The additive associations and multiplicative interaction effects of ACEs and PGSs did not change substantially when antidepressants and CRP-related medications were removed from the models.

1. *Additive interaction effects*

We calculated interaction effects between ACEs and PGSs on the additive scale to measure the extent to which the effect of the two risk factors together exceeded the effect of each considered individually (sTable 6). It has been suggested that additive interactions correspond more closely to tests for mechanistic interaction (i.e. both exposures together turn the outcome, while the removal of one turns the outcome off), rather than merely statistical interaction.13 Most multiplicative interaction effects between ACEs and MDD PGS on depression trajectories found in the main analysis (sTable 2) were also significant on the additive scale (sTable 6). In addition, we found some positive additive interaction effects between cumulative exposure to ACEs and CRP-PGS on high depressive symptoms, which were not present on the multiplicative scale. For the outcome High CRP w2-6, the results of the additive interaction effects (sTable 6) mirrored those of the multiplicative interaction analysis (sTable 3).

1. *Complete data analysis*

All models were tested again using the samples of participants with complete data on all variables. The results of the complete data analyses are provided in sTable 7 and sTable 8. The coefficients and standard errors of the associations of ACEs and PGSs with depressive symptoms were broadly similar to those found in the main imputed data analysis. The coefficients of the associations of the risk factors with CRP were also similar to those of the imputed data analysis. However, their standard errors were larger, possibly due to the reduced sample size and lower statistical power of the complete data analysis.

1. *Differences between included and non-included ELSA participants (wave 3)*

We found significant differences in socioeconomic, health, and lifestyle characteristics between the subsamples of ELSA participants included in the study and those excluded owing to insufficient data (i.e. unavailability of at least one measure of ACEs, CRP/depressive symptoms, and genetic data). However, the magnitude of these differences was rather small (sTable 9).

1. *Differences between the analytical samples’ participants with and without missing data on Depression, CRP, and ACEs*

As expected, compared with those without missing data, participants with missing data on ACEs, Depression, or CRP were older, were less likely to be married and more likely to be windowed, were more likely to have no educational qualifications, had lower wealth, and reported a higher number of childhood socioeconomic adversities (sTable 10). This comparison corroborates the results of earlier analyses suggesting that older age and socioeconomic factors are key drivers of attrition and non-response in ELSA. As these variables were used as predictors of the missing data, the MAR assumption is likely to be met in our analysis.

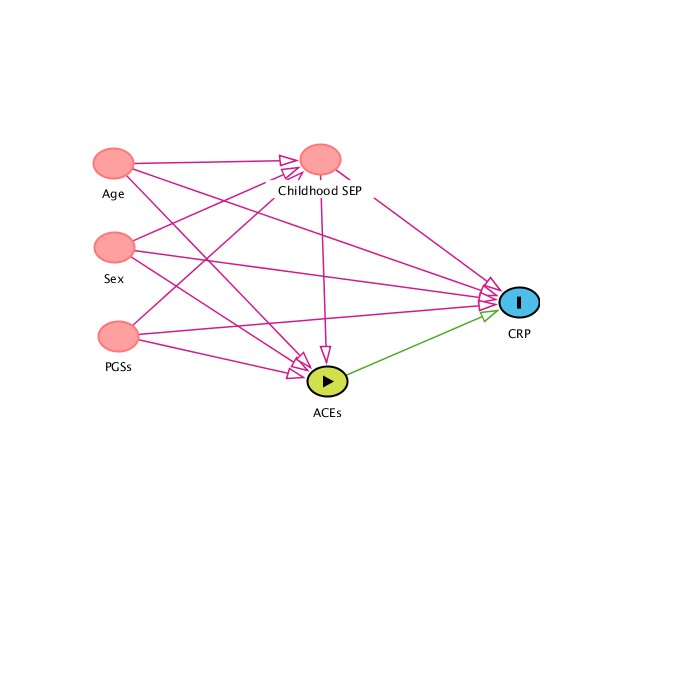
1. *Associations of ACEs and PGSs with CRP w2, excluding versus including CRP values > 10 mg/L*

Lastly, we estimated the associations of ACEs and PGSs with baseline CRP levels (wave 2), both excluding and including participants with CRP values > 10 mg/L. As shown in sTable 11, the associations did not change when participants with CRP values > 10 mg/L were included in the analysis.

A picture containing text, map

Description automatically generated

**sFigure 1. Directed Acyclic Graph of Depressive Symptoms**



**sFigure 2. Directed Acyclic Graph of C-reactive Protein**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 1. Descriptive statistics and comparison between observed and imputed data.** | | | | | | | | |
|  |  | **Depression sample** (N= 3 428) | | |  | **CRP sample** (N= 3 343) | | |
|  |  | **Observed** | **Missing** | **Imputed** |  | **Observed** | **Missing** | **Imputed** |
| *Variables* | *Levels* | *Count (%)* | *Count (%)* | *%* |  | *Count (%)* | *Count (%)* | *%* |
| **Adverse Childhood Experiences (ACEs)** | | | | | | |  |  |
| Physical abuse |  | 99(2.9) | 452(13.2) | 3.1 |  | 97(2.9) | 441(13.2) | 3.0 |
| Sexual abuse |  | 171(5) | 459(13.4) | 5.1 |  | 164(4.9) | 448(13.4) | 5.0 |
| Physical assault |  | 93(2.7) | 456(13.3) | 2.7 |  | 90(2.7) | 445(13.3) | 2.6 |
| Parent arguments |  | 703(20.5) | 487(14.2) | 21.3 |  | 685(20.5) | 478(14.3) | 21.3 |
| Low maternal bonding |  | 572(16.7) | 624(18.2) | 17.7 |  | 555(16.6) | 605(18.1) | 17.6 |
| Low paternal bonding |  | 583(17) | 699(20.4) | 18.3 |  | 568(17) | 679(20.3) | 18.2 |
| Institutionalisation |  | 55(1.6) | 3(0.1) | 1.6 |  | 53(1.6) | 3(0.1) | 1.6 |
| Separation from mother |  | 500(14.6) | 7(0.2) | 14.6 |  | 481(14.4) | 7(0.2) | 14.4 |
| Foster care/Adoption |  | 62(1.8) | 3(0.1) | 1.8 |  | 60(1.8) | 3(0.1) | 1.7 |
| Parent death |  | 178(5.2) | 7(0.2) | 5.2 |  | 174(5.2) | 7(0.2) | 5.2 |
| Parent mental illness/substance abuse |  | 209(6.1) | 466(13.6) | 6.3 |  | 201(6) | 455(13.6) | 6.4 |
| Parent separation/divorce |  | 182(5.3) | 7(0.2) | 5.3 |  | 177(5.3) | 7(0.2) | 5.3 |
| ACEs total score | 0 ACEs | 1 811(53) |  | 49 |  | 1 764(53) |  | 49 |
|  | 1 ACEs | 819(24) |  | 24 |  | 786(24) |  | 24 |
|  | 2 ACEs | 397(12) |  | 13 |  | 409(12) |  | 13 |
|  | 3 ACEs | 236(7) |  | 8 |  | 236(7) |  | 8 |
|  | 4 + ACEs | 165(5) |  | 6 |  | 148(4) |  | 6 |
| ACEs dimensions | Threat | 274(8) |  | 9 |  | 267(8) |  | 9 |
|  | Loss | 617(18) |  | 18 |  | 602(18) |  | 18 |
|  | Household Dysfunction | 823(24) |  | 25 |  | 802(24) |  | 25 |
|  | Low Parental Bonding | 926(27) |  | 28 |  | 903(27) |  | 28 |
| **Adult demographic and socioeconomic characteristics** | | | | | | | |  |
| Age – Mean (sd) |  | 70.7(8.5) | 0(0) | 70.7(8.5) |  | 69(8.5) | 0(0) | 69(8.5) |
| Sex: Female |  | 1 899(55.4) | 0(0) | 55.4 |  | 1 842(55.1) | 0(0) | 55.1 |
| Marital status | Married | 2 410(70.3) | 14(0.4) | 70.3 |  | 2 360(70.6) | 13(0.4) | 70.6 |
|  | Separated/Divorced | 374(10.9) |  | 10.9 |  | 361(10.8) |  | 10.8 |
|  | Widower | 476(13.9) |  | 13.9 |  | 458(13.7) |  | 13.7 |
|  | Single | 165(4.8) |  | 4.8 |  | 164(4.9) |  | 4.9 |
| Wealth quintiles | 1 (lowest) | 494(14.4) | 69(2) | 14.4 |  | 471(14.1) | 67(2) | 14.1 |
|  | 2 | 614(17.9) |  | 17.9 |  | 595(17.8) |  | 17.7 |
|  | 3 | 703(20.5) |  | 20.5 |  | 689(20.6) |  | 20.5 |
|  | 4 | 771(22.5) |  | 22.6 |  | 759(22.7) |  | 22.8 |
|  | 5 (highest) | 843(24.6) |  | 24.7 |  | 829(24.8) |  | 24.8 |
| Degree: Yes |  | 569(16.6) | 17(0.5) | 16.6 |  | 562(16.8) | 17(0.5) | 16.7 |
| **Childhood socioeconomic (SE) indicators** | |  |  |  |  |  |  |  |
| Overcrowding |  | 641(18.7) | 141(4.1) | 18.7 |  | 618(18.5) | 134(4) | 18.6 |
| No books when aged 10 |  | 864(25.2) | 161(4.7) | 25.3 |  | 836(25) | 157(4.7) | 25.1 |
| Manual occupation (father) |  | 27(0.8) | 7(0.2) | 0.8 |  | 27(0.8) | 7(0.2) | 0.8 |
| Financial hardship |  | 223(6.5) | 466(13.6) | 6.6 |  | 214(6.4) | 455(13.6) | 6.4 |
| Parent unemployment |  | 278(8.1) | 470(13.7) | 8.2 |  | 271(8.1) | 455(13.6) | 8.3 |
| One or more SE adversity |  | 1450(42.31) | 639(18.64) | 43.27 |  | 1424(42.6) | 632(18.91) | 42.64 |
| **Depressive symptoms – Mean (sd)** | |  |  |  |  |  |  |  |
| w1 | | 1.3(1.8) | 257(7.5) | 1.3(1.8) |  |  |  |  |
| w2 | | 1.3(1.8) | 267(7.8) | 1.4(1.8) |  |  |  |  |
| w3 | | 1.3(1.8) | 21(0.6) | 1.3(1.8) |  |  |  |  |
| w4 | | 1.2(1.8) | 82(2.4) | 1.2(1.8) |  |  |  |  |
| w5 | | 1.3(1.8) | 99(2.9) | 1.3(1.8) |  |  |  |  |
| w6 | | 1.2(1.8) | 27(0.8) | 1.2(1.8) |  |  |  |  |
| w7 | | 1.3(1.8) | 415(12.1) | 1.3(1.8) |  |  |  |  |
| w8 | | 1.3(1.8) | 734(21.4) | 1.3(1.8) |  |  |  |  |
| **C-reactive Protein (CRP)** | |  |  |  |  |  |  |  |
| High CRP repeated exposure w2,4,6 | 0 exposures |  |  |  |  | 1 972(59) |  | 53 |
|  | 1 exposure |  |  |  |  | 669(20) |  | 21 |
|  | 2 exposures |  |  |  |  | 401(12) |  | 14 |
|  | 3 exposures |  |  |  |  | 301(9) |  | 12 |
| **Medication Use** |  |  |  |  |  |  |  |  |
| Anti-inflammatory/ antihypertensive drugs | |  |  |  |  | 1 651(49.4) | 0(0) | 49.4 |
| Antidepressants |  | 343(10) | 0(0) | 10 |  |  |  |  |
| ***Note.*** Sample = ELSA, w1-w8. Sd=standard deviation. ACEs=adverse childhood experiences. CRP=C-reactive protein. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 2. G+E Additive and GxE Multiplicative Interaction Effects of ACEs and PGSs on Depression Trajectories.** | | | | | | | | |
|  | **Moderate vs Low Depression Trajectory** | | | | **High vs Low Depression Trajectory** | | | |
| **Model 1 - G+E Additive effects** | *OR* | *95%CI* | *Effect size* | *E-value*  *(lower CI)* | *OR* | *95%CI* | *Effect size* | *E-value*  *(lower CI)* |
| MDD PGS | **1.17** | **1.08;1.27** | 0.04 | 1.37 (1.24) | **1.47** | **1.28;1.70** | 0.09 | 2.30 (1.87) |
| CRP PGS | 0.99 | 0.91;1.08 | 0.00 | - | 0.97 | 0.84;1.12 | -0.01 | - |
| ACE total score | **1.17** | **1.09;1.25** | 0.04 | 1.38 (1.26) | **1.44** | **1.30;1.60** | 0.09 | 2.24 (1.92) |
| Threat | **1.64** | **1.17;2.29** | 0.12 | 1.88 (1.38) | **2.93** | **1.86;4.62** | 0.26 | 5.31 (3.13) |
| Loss | 1.23 | 0.99;1.52 | 0.05 | - | **1.70** | **1.20;2.41** | 0.13 | 2.79 (1.69) |
| Household Dysfunction | **1.42** | **1.17;1.74** | 0.08 | 1.67 (1.38) | **2.52** | **1.80;3.51** | 0.22 | 4.48 (3.00) |
| Low Parental Bonding | **1.50** | **1.22;1.83** | 0.10 | 1.75 (1.44) | **2.36** | **1.70;3.28** | 0.21 | 4.15 (2.79) |
| **Model 2 - GxE Interaction effects** | *OR* | *95%CI* |  |  | *OR* | *95%CI* |  |  |
| **ACEs x MDD PGS** |  |  |  |  |  |  |  |  |
| ACE total score | **1.17** | **1.09;1.26** | 0.04 |  | **1.43** | **1.29;1.60** | 0.09 |  |
| MDD PGS | 1.02 | 0.98;1.08 | 0.00 |  | 1.06 | 0.98;1.15 | 0.01 |  |
| ACE tot x MDD PGS | **1.10** | **1.03;1.17** | 0.02 |  | **1.13** | **1.04;1.23** | 0.03 |  |
| Threat | **1.64** | **1.17;2.30** | 0.12 |  | **2.76** | **1.70;4.50** | 0.24 |  |
| MDD PGS | **1.04** | **1.00;1.09** | 0.01 |  | **1.09** | **1.01;1.18** | 0.02 |  |
| Threat x MDD PGS | 1.15 | 0.82;1.62 | 0.03 |  | 1.46 | 0.95;2.25 | 0.09 |  |
| Loss | **1.25** | **1.01;1.55** | 0.05 |  | **1.65** | **1.16;2.36** | 0.12 |  |
| MDD PGS | 1.04 | 0.99;1.09 | 0.01 |  | **1.09** | **1.01;1.18** | 0.02 |  |
| Loss x MDD PGS | **1.30** | **1.06;1.60** | 0.06 |  | **1.52** | **1.09;2.11** | 0.10 |  |
| Household Dysfunction | **1.42** | **1.16;1.74** | 0.08 |  | **2.45** | **1.75;3.44** | 0.22 |  |
| MDD PGS | 1.03 | 0.98;1.08 | 0.01 |  | 1.07 | 0.99;1.16 | 0.02 |  |
| Household Dysfunction x MDD PGS | **1.29** | **1.07;1.55** | 0.06 |  | **1.48** | **1.15;1.9** | 0.09 |  |
| Low Parental Bonding | **1.51** | **1.23;1.84** | 0.10 |  | **2.28** | **1.63;3.20** | 0.20 |  |
| MDD PGS | 1.03 | 0.98;1.08 | 0.01 |  | 1.07 | 0.98;1.15 | 0.02 |  |
| Low Parental Bonding x MDD PGS | **1.21** | **1.01;1.44** | 0.04 |  | **1.47** | **1.15;1.89** | 0.09 |  |
| **ACEs x CRP PGS** |  |  |  |  |  |  |  |  |
| ACE total score | **1.20** | **1.01;1.42** | 0.04 |  | **1.44** | **1.14;1.81** | 0.09 |  |
| CRP PGS | 0.99 | 0.92;1.06 | 0.00 |  | 0.98 | 0.86;1.12 | 0.00 |  |
| ACE tot x CRP PGS | 0.99 | 0.94;1.05 | 0.00 |  | 1.01 | 0.94;1.08 | 0.00 |  |
| Threat | **2.68** | **1.21;5.97** | 0.24 |  | **4.40** | **1.35;14.35** | 0.36 |  |
| CRP PGS | 0.99 | 0.93;1.05 | 0.00 |  | 0.99 | 0.89;1.10 | 0.00 |  |
| Threat x CRP PGS | 0.86 | 0.68;1.09 | -0.04 |  | 0.90 | 0.64;1.26 | -0.03 |  |
| Loss | 1.27 | 0.77;2.10 | 0.06 |  | 1.79 | 0.82;3.90 | 0.14 |  |
| CRP PGS | 0.98 | 0.92;1.05 | 0.00 |  | 0.99 | 0.89;1.11 | 0.00 |  |
| Loss x CRP PGS | 0.99 | 0.85;1.15 | 0.00 |  | 0.98 | 0.77;1.25 | 0.00 |  |
| Household Dysfunction | 1.34 | 0.84;2.14 | 0.07 |  | **2.89** | **1.41;5.93** | 0.25 |  |
| CRP PGS | 0.98 | 0.92;1.04 | 0.00 |  | 1.01 | 0.89;1.14 | 0.00 |  |
| Household Dysfunction x CRP PGS | 1.03 | 0.89;1.18 | 0.01 |  | 0.96 | 0.77;1.20 | -0.01 |  |
| Low Parental Bonding | 1.52 | 0.96;2.40 | 0.10 |  | **2.64** | **1.29;5.42** | 0.23 |  |
| CRP PGS | 0.98 | 0.92;1.05 | 0.00 |  | 1.01 | 0.89;1.15 | 0.00 |  |
| Low Parental Bonding x CRP PGS | 1.00 | 0.87;1.15 | 0.00 |  | 0.98 | 0.78;1.22 | 0.00 |  |
| ***Note.*** Sample = ELSA, w1-w8 (N=3,428). Pooled estimates across 20 imputed datasets from latent class growth mixture modelling with multinomial logistic regression analysis. The odds ratios represent the Moderate or High Depression trajectory compared with the Low trajectory. Associations adjusted for sex, age, childhood socioeconomic position, use of antidepressant medications, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; OR=odds ratio; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 1). | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 3. G+E Additive and GxE Multiplicative Interaction Effects of ACEs and PGSs on High CRP w4 and Repeated Exposure to High CRP w2-6.** | | | | | | | | |
|  | **High CRP w4** | | | | **Repeated exposure to High CRP w2-6** | | | |
| **Model 1 - G+E Additive effects** | *OR* | *95% CI* | *Effect size* | *E-value*  *(lower CI)* | *OR* | *95% CI* | *Effect size* | *E-value*  *(lower CI)* |
| CRP PGS | **1.05** | **1.03;1.06** | 0.01 | 1.18 (1.14) | **1.04** | **1.03;1.06** | 0.01 | 1.16 (1.14) |
| MDD PGS | **1.06** | **1.04;1.07** | 0.01 | 1.20 (1.16) | **1.03** | **1.01;1.04** | 0.01 | 1.14 (1.08) |
| ACE total score | **1.10** | **1.09;1.11** | 0.02 | 1.28 (1.26) | **1.08** | **1.07;1.09** | 0.02 | 1.24 (1.22) |
| Threat | **1.13** | **1.07;1.18** | 0.03 | 1.32 (1.22) | **1.08** | **1.03;1.14** | 0.02 | 1.24 (1.13) |
| Loss | **1.28** | **1.24;1.32** | 0.06 | 1.52 (1.47) | **1.20** | **1.16;1.25** | 0.04 | 1.42 (1.37) |
| Household Dysfunction | **1.14** | **1.11;1.18** | 0.03 | 1.34 (1.29) | **1.13** | **1.09;1.17** | 0.03 | 1.32 (1.26) |
| Low Parental Bonding | **1.19** | **1.16;1.23** | 0.04 | 1.41 (1.37) | **1.04** | **1.04;1.05** | 0.01 | 1.16 (1.16) |
| **Model 2 - GxE Interaction effects** | *OR* | *95%CI* |  |  | *OR* | *95%CI* |  |  |
| **ACEs x CRP PGS** |  |  |  |  |  |  |  |  |
| ACE total score | **1.10** | **1.09;1.11** | 0.02 |  | **1.08** | **1.07;1.10** | 0.02 |  |
| CRP PGS | **1.02** | **1.00;1.04** | 0.00 |  | **1.03** | **1.01;1.05** | 0.01 |  |
| ACE tot x CRP PGS | **1.02** | **1.01;1.04** | 0.00 |  | **1.02** | **1.01;1.03** | 0.00 |  |
| Threat | **1.13** | **1.08;1.19** | 0.03 |  | **1.09** | **1.04;1.15** | 0.02 |  |
| CRP PGS | **1.03** | **1.01;1.05** | 0.01 |  | **1.03** | **1.02;1.05** | 0.01 |  |
| Threat x CRP PGS | **1.19** | **1.13;1.26** | 0.04 |  | **1.11** | **1.05;1.17** | 0.03 |  |
| Loss | **1.28** | **1.24;1.32** | 0.06 |  | **1.20** | **1.16;1.25** | 0.04 |  |
| CRP PGS | **1.04** | **1.03;1.06** | 0.01 |  | **1.04** | **1.03;1.06** | 0.01 |  |
| Loss x CRP PGS | 1.00 | 0.96;1.04 | 0.00 |  | 0.98 | 0.95;1.02 | 0.00 |  |
| Household Dysfunction | **1.15** | **1.12;1.19** | 0.03 |  | **1.13** | **1.10;1.17** | 0.03 |  |
| CRP PGS | **1.04** | **1.02;1.06** | 0.01 |  | **1.04** | **1.02;1.06** | 0.01 |  |
| Household Dysfunction x CRP PGS | 1.00 | 0.97;1.04 | 0.00 |  | 1.01 | 0.98;1.04 | 0.00 |  |
| Low Parental Bonding | **1.20** | **1.17;1.24** | 0.04 |  | **1.04** | **1.04;1.05** | 0.01 |  |
| CRP PGS | **1.03** | **1.01;1.05** | 0.01 |  | 1.01 | 0.99;1.03 | 0.00 |  |
| Low Parental Bonding x CRP PGS | **1.06** | **1.03;1.10** | 0.01 |  | **1.01** | **1.01;1.02** | 0.00 |  |
| **ACEs x MDD PGS** |  |  |  |  |  |  |  |  |
| ACE total score | **1.10** | **1.09;1.11** | 0.02 |  | **1.08** | **1.07;1.09** | 0.02 |  |
| MDD PGS | **1.07** | **1.05;1.09** | 0.02 |  | **1.03** | **1.01;1.05** | 0.01 |  |
| ACE tot x MDD PGS | 0.99 | 0.98;1.00 | 0.00 |  | 1.00 | 0.99;1.01 | 0.00 |  |
| Threat | **1.13** | **1.08;1.19** | 0.03 |  | **1.09** | **1.04;1.15** | 0.02 |  |
| MDD PGS | **1.07** | **1.05;1.08** | 0.02 |  | **1.04** | **1.02;1.05** | 0.01 |  |
| Threat x MDD PGS | 0.97 | 0.91;1.03 | -0.01 |  | 0.97 | 0.93;1.02 | -0.01 |  |
| Loss | **1.28** | **1.24;1.33** | 0.06 |  | **1.20** | **1.16;1.25** | 0.04 |  |
| MDD PGS | **1.08** | **1.06;1.10** | 0.02 |  | **1.06** | **1.04;1.08** | 0.01 |  |
| Loss x MDD PGS | **0.92** | **0.88;0.96** | -0.02 |  | **0.88** | **0.85;0.91** | -0.03 |  |
| Household Dysfunction | **1.14** | **1.11;1.18** | 0.03 |  | **1.12** | **1.08;1.16** | 0.03 |  |
| MDD PGS | **1.06** | **1.04;1.08** | 0.01 |  | **1.02** | **1.00;1.03** | 0.00 |  |
| Household Dysfunction x MDD PGS | 0.99 | 0.95;1.03 | 0.00 |  | **1.05** | **1.02;1.09** | 0.01 |  |
| Low Parental Bonding | **1.19** | **1.15;1.22** | 0.04 |  | **1.04** | **1.03;1.04** | 0.01 |  |
| MDD PGS | **1.04** | **1.02;1.06** | 0.01 |  | 1.00 | 0.98;1.02 | 0.00 |  |
| Low Parental Bonding x MDD PGS | **1.06** | **1.02;1.10** | 0.01 |  | **1.01** | **1.01;1.02** | 0.00 |  |
| ***Note.*** Sample = ELSA, w1-w8 (N=3,343). Pooled estimates across 20 imputed datasets from ordinal logistic regression analysis. The odds ratios represent the likelihood of high CRP levels (≥ 3 mg/L) at wave 4 and of repeated exposure to high CRP across waves 2, 4, and 6. Associations adjusted for sex, age, childhood socioeconomic position, use of anti-inflammatory/antihypertensive medications, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; OR=odds ratio; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 1). | | | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **sTable 4. Predicted probabilities of the outcomes according to different values of the risk factors.** | | | | |
|  | **Probability of high depressive symptoms** | | **Probability of high CRP on one or more occasions** | |
|  | **Men** | **Women** | **Men** | **Women** |
| **Main effects** | |  |  |  |
| ***MDD-PGSa*** |  |  |  |  |
| Low (10% percentile) | 0.02 | 0.07 | 0.53 | 0.56 |
| High (90% percentile) | 0.06 | 0.18 | 0.54 | 0.57 |
| % increase | 4% | 11% | 1% | 1% |
| ***CRP-PGSb*** |  |  |  |  |
| Low (10% percentile) | 0.04 | 0.11 | 0.52 | 0.55 |
| High (90% percentile) | 0.03 | 0.10 | 0.54 | 0.57 |
| % increase | -1% | -1% | 2% | 2% |
| **ACEsc** |  |  |  |  |
| 0 ACEs | 0.04 | 0.11 | 0.53 | 0.56 |
| 4 ACEs | 0.14 | 0.34 | 0.57 | 0.60 |
| % increase | 10% | 23% | 4% | 4% |
| **GxE effects** |  |  |  |  |
| ***ACEs x MDD-PGSd*** | |  |  |  |
| 0 ACEs and low PGS | 0.03 | 0.09 |  |  |
| 4 ACEs and high PGS | 0.26 | 0.53 |  |  |
| % increase | 23% | 44% |  |  |
| ***ACEs x CRP-PGSe*** |  |  |  |  |
| 0 ACEs and low PGS |  |  | 0.52 | 0.56 |
| 4 ACEs and high PGS |  |  | 0.58 | 0.61 |
| % increase |  |  | 6% | 5% |
| ***Threat x CRP-PGSe*** |  |  |  |  |
| 0 Threat  and low PGS |  |  | 0.52 | 0.56 |
| 1 Threat and high PGS |  |  | 0.66 | 0.68 |
| % increase |  |  | 14% | 12% |
| Note. Predicted probabilities from multinomial (depression) and ordinal (CRP) logistic regression models adjusted for all covariates.  a Predicted probability for a man/woman with 0 ACEs, average CRP-PGS, average age, no childhood socioeconomic adversity, and no use of antidepressant/CRP medications.  b Predicted probability for a man/woman with 0 ACEs, average MDD-PGS, average age, no childhood socioeconomic adversity, and no use of antidepressant/CRP medications.  c Predicted probability for a man/woman with average MDD-PGS, average CRP-PGS, average age, no childhood socioeconomic adversity, and no use of antidepressant/CRP medications.  d Predicted probability for a man/woman with average CRP-PGS, average age, no childhood socioeconomic adversity, and no use of antidepressant/CRP medications.  e Predicted probability for a man/woman with average MDD-PGS, average age, no childhood socioeconomic adversity, and no use of antidepressant/CRP medications. | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| sTable 5. G+E Additive and GxE Multiplicative Interaction Effects of ACEs and PGSs on Depression Trajectories and High CRP w2-6 without adjustment for antidepressant and CRP-related medications. | | | | | | | |
|  | | **Moderate Depression Trajectory (vs Low)** | | **High Depression Trajectory (vs Low)** | | **High CRP w2-6** | |
| Model 1 - G+E Additive effects | | *OR* | *95% CI* | *OR* | *95% CI* | *OR* | *95% CI* |
| MDD PGS |  | **1.18** | **1.09;1.28** | **1.52** | **1.31;1.75** | **1.02** | **1.01;1.04** |
| CRP PGS |  | 0.99 | 0.92;1.08 | 0.98 | 0.85;1.13 | **1.03** | **1.02;1.04** |
| ACE total score | | **1.17** | **1.09;1.25** | **1.46** | **1.32;1.61** | **1.08** | **1.07;1.09** |
| Threat |  | **1.69** | **1.21;2.35** | **3.21** | **2.10;4.93** | **1.08** | **1.02;1.13** |
| Loss |  | 1.18 | 0.95;1.46 | **1.52** | **1.08;2.14** | **1.21** | **1.17;1.26** |
| Household Dysfunction | | **1.44** | **1.18;1.76** | **2.58** | **1.86;3.59** | **1.11** | **1.08;1.15** |
| Low Parental Bonding | | **1.54** | **1.26;1.88** | **2.50** | **1.81;3.45** | **1.04** | **1.03;1.04** |
| Model 2 - GxE Interaction effects | | |  |  |  |  |  |
| ACEs x MDD PGS | |  |  |  |  |  |  |
| ACE total score | | **1.17** | **1.09;1.26** | **1.45** | **1.30;1.60** | **1.08** | **1.07;1.09** |
| MDD PGS |  | 1.02 | 0.97;1.07 | 1.06 | 0.98;1.15 | **1.02** | **1.01;1.04** |
| ACE tot x MDD PGS | | **1.10** | **1.03;1.17** | **1.15** | **1.06;1.24** | 1.00 | 0.99;1.01 |
| Threat |  | **1.68** | **1.20;2.34** | **3.00** | **1.90;4.73** | **1.08** | **1.03;1.14** |
| MDD PGS |  | 1.04 | 0.99;1.09 | **1.10** | **1.01;1.18** | **1.03** | **1.02;1.04** |
| Threat x MDD PGS | | 1.19 | 0.85;1.65 | **1.55** | **1.02;2.35** | 0.98 | 0.94;1.04 |
| Loss |  | 1.20 | 0.97;1.49 | **1.46** | **1.03;2.06** | **1.21** | **1.17;1.26** |
| MDD PGS |  | 1.04 | 0.99;1.09 | **1.10** | **1.02;1.18** | **1.05** | **1.04;1.07** |
| Loss x MDD PGS | | **1.33** | **1.09;1.64** | **1.65** | **1.19;2.29** | **0.88** | **0.85;0.91** |
| Household Dysfunction | | **1.44** | **1.17;1.75** | **2.50** | **1.79;3.50** | **1.11** | **1.07;1.15** |
| MDD PGS |  | 1.03 | 0.98;1.08 | 1.07 | 0.99;1.16 | **1.01** | **1.00;1.03** |
| Household Dysfunction x MDD PGS | | **1.30** | **1.09;1.56** | **1.53** | **1.20;1.95** | **1.04** | **1.01;1.08** |
| Low Parental Bonding | | **1.55** | **1.26;1.90** | **2.48** | **1.78;3.47** | **1.04** | **1.03;1.04** |
| MDD PGS |  | **1.10** | **1.03;1.17** | **1.27** | **1.12;1.43** | 0.99 | 0.97;1.01 |
| Low Parental Bonding x MDD PGS | | 1.09 | 0.89;1.33 | 1.15 | 0.85;1.56 | **1.01** | **1.01;1.02** |
| ACEs x CRP PGS | |  |  |  |  |  |  |
| ACE total score | | **1.21** | **1.02;1.44** | **1.48** | **1.18;1.85** | **1.08** | **1.07;1.09** |
| CRP PGS |  | 0.99 | 0.92;1.06 | 0.99 | 0.87;1.13 | 1.01 | 0.99;1.03 |
| ACE tot x CRP PGS | | 0.99 | 0.94;1.04 | 1.00 | 0.93;1.07 | **1.01** | **1.01;1.02** |
| Threat |  | **2.76** | **1.24;6.12** | **4.72** | **1.55;14.37** | **1.08** | **1.03;1.14** |
| CRP PGS |  | 0.99 | 0.93;1.05 | 0.99 | 0.89;1.11 | **1.02** | **1.01;1.03** |
| Threat x CRP PGS | | 0.86 | 0.67;1.09 | 0.90 | 0.65;1.24 | **1.10** | **1.05;1.16** |
| Loss |  | 1.26 | 0.76;2.08 | 1.69 | 0.78;3.65 | **1.21** | **1.17;1.26** |
| CRP PGS |  | 0.98 | 0.92;1.05 | 1.00 | 0.90;1.11 | **1.03** | **1.02;1.05** |
| Loss x CRP PGS | | 0.97 | 0.84;1.13 | 0.96 | 0.75;1.22 | 0.97 | 0.93;1.01 |
| Household Dysfunction | | 1.36 | 0.86;2.16 | **3.01** | **1.50;6.02** | **1.12** | **1.08;1.16** |
| CRP PGS |  | 0.98 | 0.92;1.04 | 1.01 | 0.90;1.15 | **1.02** | **1.01;1.04** |
| Household Dysfunction x CRP PGS | | 1.02 | 0.89;1.17 | 0.96 | 0.77;1.18 | 1.01 | 0.98;1.05 |
| Low Parental Bonding | | **1.58** | **1.01;2.50** | **3.08** | **1.55;6.11** | **1.04** | **1.04;1.04** |
| CRP PGS |  | 0.98 | 0.92;1.05 | 1.02 | 0.90;1.15 | 1.00 | 0.98;1.02 |
| Low Parental Bonding x CRP PGS | | 0.99 | 0.86;1.14 | 0.94 | 0.76;1.17 | **1.01** | **1.01;1.02** |
| *Note.* Sample = ELSA, w1-w8 (Depression: N=3,428; CRP: N=3,343). Pooled estimates across 20 imputed datasets from latent class growth mixture modelling with multinomial logistic regression analysis (depression) and ordinal logistic regression analysis (CRP). Associations adjusted for sex, age, childhood socioeconomic position, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; OR=odds ratio; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 1). | | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| sTable 6. Interaction effects between ACEs and PGSs on the additive scale. | | | | | | |
|  | **Moderate Depressive-symptom trajectory (vs Low)** | | **High Depressive-symptom trajectory (vs Low)** | | **High CRP w2-6** | |
|  | *Coef.* | *95% CI* | *Coef.* | *95% CI* | *Coef.* | *95% CI* |
| MDD PGS x ACE Total score (ref: 0 ACEs) | | | | | | |
| 1 ACE | **0.41** | **0.30;0.52** | **3.74** | **3.06;4.41** | 0.04 | -0.03;0.10 |
| 2 ACEs | **0.94** | **0.67;1.21** | **10.39** | **8.46;12.32** | 0.08 | -0.06;0.22 |
| 3 ACEs | **0.94** | **0.67;1.21** | **10.39** | **8.46;12.32** | 0.13 | -0.11;0.36 |
| 4 ACEs | **2.54** | **1.71;3.37** | **42.94** | **33.33;52.54** | 0.18 | -0.15;0.51 |
| MDD PGS x Threat | **1.28** | **0.33;2.22** | **27.51** | **18.4;36.62** | 0.17 | -0.20;0.54 |
| MDD PGS x Loss | **1.03** | **0.56;1.50** | **11.78** | **8.3;15.25** | **-0.70** | **-1.02;-0.38** |
| MDD PGS x Household Dysfunction | **0.95** | **0.51;1.40** | **11.31** | **8.18;14.43** | **0.35** | **0.12;0.57** |
| MDD PGS x Bonding | 0.09 | -0.44;0.62 | **10.37** | **6.93;13.81** | **0.44** | **0.22;0.66** |
| CRP PGS x ACE Total score (ref: 0 ACEs) | | | | | | |
| 1 ACE | 0.04 | -0.03;0.12 | **0.22** | **0.09;0.35** | **0.08** | **0.02;0.15** |
| 2 ACEs | 0.11 | -0.06;0.28 | **0.63** | **0.24;1.01** | **0.18** | **0.04;0.32** |
| 3 ACEs | 0.20 | -0.10;0.50 | **1.37** | **0.50;2.24** | **0.29** | **0.06;0.51** |
| 4 ACEs | 0.33 | -0.14;0.80 | **2.67** | **0.89;4.44** | **0.42** | **0.09;0.74** |
| CRP PGS x Threat | 0.11 | -0.44;0.66 | **-2.01** | **-3.83;-0.19** | **0.74** | **0.34;1.13** |
| CRP PGS x Loss | **0.60** | **0.36;0.83** | -0.49 | -1.24;0.26 | -0.23 | -0.52;0.05 |
| CRP PGS x Household Dysfunction | 0.23 | -0.02;0.49 | **0.79** | **0.10;1.48** | 0.02 | -0.21;0.25 |
| CRP PGS x Bonding | -0.50 | -0.82;-0.17 | -0.45 | -1.37;0.46 | **0.40** | **0.19;0.62** |
| *Note.* Sample = ELSA, w1-w8 (Depression: N=3,428; CRP: N=3,343). Additive interaction coefficients represent the relative excess risk due to interaction (RERI). See VanderWeele et al. (2014)12 for the formula and Stata code. To calculate RERI, it is necessary to compare two different levels of each exposure. For the ACEs total score, the groups of participants with 1, 2, 3, or 4 ACEs were compared with those without ACEs. For the dimension-specific ACE scores, we compared the groups of participants with and without each type of ACEs. For the MDD and CRP PGS, we selected the lowest and highest 10th percentiles of the distribution of their scores. All additive interaction effects were adjusted for sex, age, childhood socioeconomic position, use of antidepressants or anti-inflammatory/antihypertensive medications, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; Coef=coefficient; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 0). | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **sTable 7. G+E Additive and GxE Interaction Effects of ACEs and PGSs on Depression Trajectories - Complete data analysis.** | | | | |
|  | **Moderate vs Low Depression Trajectory**  **(N=2424)** | | **High vs Low Depression Trajectory**  **(N=2424)** | |
| **Model 1 - G+E Additive effects** | OR | 95%CI | OR | 95%CI |
| MDD PGS | **1.16** | **1.06;1.27** | **1.60** | **1.32;1.95** |
| CRP PGS | 1.00 | 0.91;1.10 | 1.02 | 0.86;1.22 |
| ACE total score | **1.21** | **1.11;1.32** | **1.45** | **1.28;1.65** |
| Threat | **1.76** | **1.25;2.49** | **3.23** | **1.99;5.27** |
| Loss | **1.35** | **1.07;1.70** | **1.75** | **1.16;2.63** |
| Household Dysfunction | **1.46** | **1.18;1.80** | **2.58** | **1.82;3.65** |
| Low Parental Bonding | **1.51** | **1.22;1.87** | **2.29** | **1.60;3.28** |
| **Model 2 - GxE Interaction effects** |  |  |  |  |
| **ACEs x MDD PGS** |  |  |  |  |
| ACE tot x MDD PGS | **1.13** | **1.04;1.22** | **1.19** | **1.06;1.34** |
| Threat x MDD PGS | 1.15 | 0.82;1.61 | 1.44 | 0.89;2.34 |
| Loss x MDD PGS | **1.43** | **1.15;1.79** | **1.58** | **1.08;2.30** |
| Household Dysfunction x MDD PGS | **1.29** | **1.06;1.56** | **1.43** | **1.09;1.89** |
| Low Parental Bonding x MDD PGS | **1.27** | **1.06;1.54** | **1.60** | **1.19;2.16** |
| **ACEs x CRP PGS** |  |  |  |  |
| ACE tot x CRP PGS | 0.98 | 0.92;1.04 | 1.00 | 0.91;1.09 |
| Threat x CRP PGS | 0.82 | 0.63;1.06 | 0.85 | 0.59;1.21 |
| Loss x CRP PGS | 1.03 | 0.87;1.21 | 1.01 | 0.77;1.34 |
| Household Dysfunction x CRP PGS | 1.01 | 0.87;1.16 | 0.92 | 0.73;1.17 |
| Low Parental Bonding x CRP PGS | 0.99 | 0.85;1.14 | 0.92 | 0.72;1.18 |
| ***Note.*** Sample = ELSA, w1-w8. Estimates from latent class growth mixture modelling with multinomial logistic regression analysis. The odds ratios represent the Moderate or High Depression trajectory compared with the Low trajectory. Associations adjusted for sex, age, childhood socioeconomic position, use of antidepressant medications, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; OR=odds ratio; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 1). | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **sTable 8. G+E Additive and GxE Interaction Effects of ACEs and PGSs on High CRP w4 and Repeated Exposure to High CRP w2-6 – Complete data analysis.** | | | | |
|  | **High CRP w4**  **(N=2167)** | | **Repeated exposure to high CRP w2-6 (N=1416)** | |
| **Model 1 – G+E Additive effects** | *OR* | *95% CI* | *OR* | *95% CI* |
| CRP PGS | 1.05 | 0.96;1.15 | 1.03 | 0.93;1.14 |
| MDD PGS | 1.07 | 0.98;1.17 | 1.02 | 0.92;1.13 |
| ACE tot | **1.08** | **1.04;1.12** | **1.06** | **1.02;1.10** |
| Threat | 1.25 | 0.91;1.59 | 0.98 | 0.59;1.37 |
| Loss | **1.51** | **1.26;1.75** | **1.42** | **1.15;1.69** |
| Household Dysfunction | **1.28** | **1.06;1.49** | **1.21** | **0.97;1.46** |
| Low Parental Bonding | **1.06** | **1.02;1.10** | **1.08** | **1.04;1.12** |
| **Model 2 – GxE Interaction effects** |  |  |  |  |
| **ACEs x CRP PGS** |  |  |  |  |
| ACE tot x CRP PGS | 1.02 | 0.98;1.06 | **1.05** | **1.01;1.10** |
| Threat x CRP PGS | 1.25 | 0.87;1.63 | 1.16 | 0.69;1.62 |
| Loss x CRP PGS | 1.10 | 0.85;1.35 | 1.08 | 0.80;1.35 |
| Household Dysfunction x CRP PGS | 0.99 | 0.77;1.20 | 1.11 | 0.87;1.35 |
| Low Parental Bonding x CRP PGS | 1.01 | 0.97;1.05 | **1.05** | **1.00;1.09** |
| **ACEs x MDD PGS** |  |  |  |  |
| ACE tot x MDD PGS | 1.00 | 0.96;1.04 | 0.99 | 0.95;1.04 |
| Threat x MDD PGS | 0.86 | 0.51;1.21 | 0.78 | 0.38;1.19 |
| Loss x MDD PGS | 0.86 | 0.61;1.10 | 0.95 | 0.67;1.23 |
| Household Dysfunction x MDD PGS | 0.98 | 0.76;1.20 | 0.98 | 0.73;1.22 |
| Low Parental Bonding x MDD PGS | 1.02 | 0.98;1.06 | 1.03 | 0.98;1.07 |
| ***Note.*** Sample = ELSA, w1-w8. Estimates from ordinal logistic regression analysis. The odds ratios represent the likelihood of high CRP levels (≥ 3 mg/L) at wave 4 and of repeated exposure to high CRP across waves 2, 4, and 6. Associations adjusted for sex, age, childhood socioeconomic position, use of anti-inflammatory/antihypertensive medications, and 5 principal components of population stratification. ACEs=adverse childhood experiences; PGSs=polygenic scores; CRP=C-reactive protein; MDD=major depressive disorder; OR=odds ratio; CI=confidence interval. Values presented in bold are statistically significant at the 5% level (i.e. 95% CI does not include 1). | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 9. Comparison of sample characteristics between the analytical samples and the full ELSA sample at wave 3.** | | | | | | | | | | | | | |
|  |  | **Depression sample** | | | | | | **CRP sample** | | | | | |
|  |  | **Excluded** | | **Included** | | **Group comparisons** | | **Excluded** | | **Included** | | **Group comparisons** | |
| *Variable* | *Levels* | *N* | *Mean (sd)/ %* | *N* | *Mean (sd)/ %* | *p-value\** | *r\** | *N* | *Mean (sd)/ %* | *N* | *Mean (sd)/ %* | *p-value\** | *r\** |
| Age |  | 5927 | 65.65 (11.54) | 3416 | 64.78 (8.61) | <.001 | 0.001 | 5983 | 65.64 (11.52) | 3360 | 64.77 (8.60) | <.001 | 0.001 |
| Sex | Female | 5927 | 54.8% | 3416 | 55.3% | 0.634 | 0.005 | 5983 | 54.9*%* | 3360 | 55.1% | 0.900 | 0.001 |
| Marital status | Married | 5926 | 63.8 % | 3416 | 70.3% | <.001 | 0.066 | 5982 | 63.7% | 3360 | 70.6% | <.001 | 0.069 |
|  | Separated/Divorced |  | 11.5% |  | 10.9 % |  |  |  | 11.6% |  | 10.8% |  |  |
|  | Windowed |  | 18.5% |  | 13.9% |  |  |  | 18.5% |  | 13.8% |  |  |
|  | Single |  | 6.2% |  | 4.8% |  |  |  | 6.2% |  | 4.9% |  |  |
| Educational attainment | Degree | 5890 | 15.9% | 3414 | 19.2% | <.001 | 0.042 | 5946 | 15.8% | 3358 | 19.4% | <.001 | 0.045 |
| Wealth quintiles  (1=lowest; 5=highest) | | 5736 | 2.86 (1.41) | 3360 | 3.25 (1.38) | <.001 | 0.133 | 5792 | 2.86 (1.41) | 3304 | 3.26 (1.38) | <.001 | 0.138 |
| Self-reported health  (1=very good; 5=very bad) | | 5704 | 2.24 (0.95) | 3415 | 2.01 (0.83) | <.001 | 0.113 | 5760 | 2.24 (0.95) | 3359 | 2.00 (0.82) | <.001 | 0.119 |
| Number of mobility problems (1-10) | | 5923 | 2.17 (2.73) | 3416 | 1.63 (2.29) | <.001 | 0.082 | 5979 | 2.18 (2.74) | 3360 | 1.60 (2.26) | <.001 | 0.091 |
| Smoking | Current smoker | 5849 | 21.3% | 3410 | 15.5% | <.001 | 0.055 | 5905 | 21.3% | 3354 | 15.2% | <.001 | 0.060 |
| Physical activity | Light | 5871 | 28.4% | 3390 | 14.7% | <.001 | 0.144 | 5926 | 28.5% | 3335 | 14.3% | <.001 | 0.150 |
|  | Moderate |  | 46.1% |  | 51.7% |  |  |  | 46.2% |  | 51.7% |  |  |
|  | Vigorous |  | 25.5% |  | 33.6% |  |  |  | 25.4% |  | 34.0% |  |  |
| Alcohol consumption | 5-7 days a week | 4482 | 21.3% | 3110 | 25.1% | <.001 | 0.064 | 4532 | 21.3% | 3060 | 25.2% | <.001 | 0.068 |
|  | 1-4 days a week |  | 37.1% |  | 39.6% |  |  |  | 37.0% |  | 39.8% |  |  |
|  | Less than weekly |  | 41.5% |  | 35.3% |  |  |  | 41.7% |  | 35.0% |  |  |
| ***Note****.* Sample = ELSA, w1-w8. \*p-value estimates from significance tests including t-tests (continuous variables) or chi-square tests (categorical variables). r coefficients obtained from Spearman’s Rho correlation tests. Sd=standard deviation. CRP=C-reactive protein.  a comparison based on binary variable (1=married; 0=not married). | | | | | | | | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **sTable 10. Comparison of the sociodemographic characteristics of the analytical samples’ participants with and without missing data on Depression, CRP, and ACEs.** | | | | | | |
|  | **Depression sample (N= 3428)** | | | | | |
|  | **Missing Depression Data (N=1146)** | **Complete Depression Data (N=2282)** | **p-value\*** | **Missing ACEs Data (N=855)** | **Complete ACEs Data (N=2573)** | **p-value\*** |
| **Sex** |  |  | 0.402 |  |  | 0.008 |
| Male | 523 (45.6%) | 1007 (44.1%) | | 348 (40.7%) | 1182 (45.9%) | |
| Female | 623 (54.4%) | 1275 (55.9%) | | 507 (59.3%) | 1391 (54.1%) | |
| **Age** |  |  | 0.001 |  |  | 0.365 |
| Mean (SD) | 71.387 (10.575) | 70.379 (7.258) | | 70.945 (8.676) | 70.640 (8.473) | |
| Range | 49.000 - 90.000 | 42.000 - 90.000 | | 42.000 - 90.000 | 49.000 - 90.000 | |
| **Marital Status** |  |  | < 0.001 |  |  | < 0.001 |
| Married/civil partnership | 766 (67.4%) | 1637 (71.8%) | | 536 (63.0%) | 1867 (72.8%) | |
| Separated/divorced | 108 (9.5%) | 264 (11.6%) |  | 117 (13.7%) | 255 (9.9%) |  |
| Single | 64 (5.6%) | 101 (4.4%) |  | 51 (6.0%) | 114 (4.4%) |  |
| Widowed | 199 (17.5%) | 277 (12.2%) |  | 147 (17.3%) | 329 (12.8%) |  |
| **Education** |  |  | < 0.001 |  |  | < 0.001 |
| A-levels | 276 (24.3%) | 597 (26.2%) |  | 206 (24.2%) | 667 (26.0%) |  |
| Degree | 204 (18.0%) | 451 (19.8%) |  | 127 (14.9%) | 528 (20.6%) |  |
| Foreign/other | 90 (7.9%) | 195 (8.6%) |  | 79 (9.3%) | 206 (8.0%) |  |
| GCSE | 242 (21.3%) | 559 (24.5%) |  | 186 (21.9%) | 615 (24.0%) |  |
| No qualification | 323 (28.5%) | 477 (20.9%) |  | 253 (29.7%) | 547 (21.3%) |  |
| **Number of childhood socioeconomic adversities** | | | < 0.001 |  |  | < 0.001 |
| Mean (SD) | 0.660 (0.828) | 0.539 (0.752) | | 0.748 (0.840) | 0.555 (0.768) | |
| Range | 0.000 - 4.000 | 0.000 - 4.000 | | 0.000 - 3.000 | 0.000 - 4.000 | |
| **Wealth quintiles** |  |  | < 0.001 |  |  | < 0.001 |
| Mean (SD) | 2.919 (1.361) | 3.209 (1.353) | | 2.918 (1.362) | 3.176 (1.357) | |
| Range | 1.000 - 5.000 | 1.000 - 5.000 | | 1.000 - 5.000 | 1.000 - 5.000 | |
|  | **CRP Sample (N=3343)** | | | | | |
|  | **Missing CRP Data (N=1596)** | **Complete CRP Data (N=1747)** | **p value** | **Missing ACEs Data (N=833)** | **Complete ACEs Data (N=2510)** | **p value** |
| **Sex** |  |  | 0.111 |  |  | 0.008 |
| Male | 739 (46.3%) | 761 (43.6%) |  | 341 (40.9%) | 1159 (46.2%) | |
| Female | 857 (53.7%) | 986 (56.4%) |  | 492 (59.1%) | 1351 (53.8%) | |
| **Age** |  |  | 0.418 |  |  | 0.263 |
| Mean (SD) | 70.580 (9.437) | 70.819 (7.570) | | 70.990 (8.631) | 70.610 (8.472) | |
| Range | 42.000 - 90.000 | 60.000 - 90.000 | | 42.000 - 90.000 | 49.000 - 90.000 | |
| **Marital Status** |  |  | 0.392 |  |  | < 0.001 |
| Married/civil partnership | 1101 (69.5%) | 1251 (71.6%) | | 526 (63.4%) | 1826 (73.0%) | |
| Separated/divorced | 172 (10.9%) | 186 (10.7%) |  | 111 (13.4%) | 247 (9.9%) |  |
| Single | 77 (4.9%) | 85 (4.9%) |  | 51 (6.2%) | 111 (4.4%) |  |
| Widowed | 235 (14.8%) | 224 (12.8%) |  | 141 (17.0%) | 318 (12.7%) |  |
| **Education** |  |  | 0.704 |  |  | < 0.001 |
| A-levels | 398 (25.1%) | 459 (26.3%) |  | 201 (24.2%) | 656 (26.2%) |  |
| Degree | 302 (19.1%) | 344 (19.7%) |  | 125 (15.1%) | 521 (20.8%) |  |
| Foreign/other | 138 (8.7%) | 141 (8.1%) |  | 77 (9.3%) | 202 (8.1%) |  |
| GCSE | 368 (23.2%) | 416 (23.8%) |  | 183 (22.1%) | 601 (24.0%) |  |
| No qualification | 377 (23.8%) | 386 (22.1%) |  | 243 (29.3%) | 520 (20.8%) |  |
| **Number of childhood socioeconomic adversities** | | | 0.233 |  |  | < 0.001 |
| Mean (SD) | 0.555 (0.761) | 0.590 (0.791) | | 0.741 (0.841) | 0.548 (0.764) | |
| Range | 0.000 - 4.000 | 0.000 - 4.000 | | 0.000 - 3.000 | 0.000 - 4.000 | |
| **Wealth quintiles** |  |  | 0.003 |  |  | < 0.001 |
| Mean (SD) | 3.054 (1.373) | 3.195 (1.340) | | 2.934 (1.357) | 3.192 (1.352) | |
| Range | 1.000 - 5.000 | 1.000 - 5.000 | | 1.000 - 5.000 | 1.000 - 5.000 | |
| ***Note.*** \*p-value estimates from significance tests including t-tests (continuous variables) or chi-square tests (categorical variables). SD = standard deviation. ACEs = Adverse Childhood Experiences. CRP = C-reactive protein. | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 11. Associations of ACEs and PGSs with CRP w2, excluding versus including CRP values > 10 mg/L** | | | | | | | | |
|  | **Outcome: Log CRP w2 (excluding > 10 mg/L)** | | | | **Outcome: Log CRP w2 (including > 10 mg/L)** | | | |
| *Risk Factor* | *Estimate (B)* | *Standard error* | *p-value* | *Sample size* | *Estimate (B)* | *Standard error* | *p-value* | *Sample size* |
| ACEs total score | 0.043 | 0.016 | 0.008 | 2055 | 0.044 | 0.018 | 0.018 | 2514 |
| CRP-PGS | 0.010 | 0.004 | 0.018 | 2641 | 0.011 | 0.005 | 0.018 | 3100 |
| MDD-PGS | 0.002 | 0.001 | 0.028 | 2641 | 0.002 | 0.001 | 0.048 | 3100 |
| ***Note.*** Complete data analysis. | | | | | | | | |

**References**

1 Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *American journal of human genetics* **81**, 559-575, doi:10.1086/519795 (2007).

2 RStudioTeam. RStudio: Integrated Development for R. *Inc., Boston, MA* **URL** [**http://www.rstudio.com/**](http://www.rstudio.com/)**.** (2016).

3 Danecek, P. *et al.* The variant call format and VCFtools. *Bioinformatics* **27**, 2156-2158, doi:10.1093/bioinformatics/btr330 (2011).

4 Price, A. L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nature genetics* **38**, 904-909, doi:10.1038/ng1847 (2006).

5 Wang, D. *et al.* Comparison of methods for correcting population stratification in a genome-wide association study of rheumatoid arthritis: principal-component analysis versus multidimensional scaling. *BMC Proc* **3 Suppl 7**, S109 (2009).

6 Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31**, 1466-1468, doi:10.1093/bioinformatics/btu848 (2015).

7 Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539-542, doi:10.1038/nature17671 (2016).

8 Ware EB *et al.* Method of Construction Affects Polygenic Score Prediction of Common Human Trait. *BiorXiv*, 1-13 (2017).

9. Newsom, J. T. Longitudinal Structural Equation Modeling. (Taylor & Francis, 2015).

10. Herle, M. et al. Identifying typical trajectories in longitudinal data: modelling strategies and interpretations. Eur. J. Epidemiol. (2020). doi:10.1007/s10654-020-00615-6

11. Steptoe, A., Breeze, E., Banks, J., & Nazroo, J. (2013). Cohort Profile: The English Longitudinal Study of Ageing. International Journal of Epidemiology, 42(6), 1640–1648.

12. Rubin, D. B. Multiple Imputation for Nonresponse in Surveys. (John Wiley and Sons, 2004).

13. VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiol Method. 2014;3(1):33–72.