

Genetic risk of Major Depressive Disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression

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Supplementary Material

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Cohort description

Participants were sampled from the Generation Scotland: Scottish Family Health Study (GS:SFHS) – a family-based epidemiological cohort recruited at random from General Practitioners' practices throughout Scotland between 2006 and 2011 (Smith *et al.*, 2013, Smith *et al.*, 2006). During baseline assessment, participants aged 18-98 (N = 24,090, Mean = 47.64, SD = 15.41) provided a wealth of clinical, phenotypic and biological data, including personality measures such as Neuroticism and a structured interview for clinical MDD diagnosis. Blood and salivary DNA was also taken for 98% of the cohort for genome-wide genotyping (Smith *et al.*, 2006; Smith *et al.*, 2013). In September 2014, GS:SFHS participants were re-contacted and asked to take part in a follow-up assessment of mental health and resilience (Navrady *et al.*, 2017). A total of 9,618 participants aged 22-100 (Mean = 56.43, SD = 13.37) provided useable re-contact data including questionnaire measures of self-reported MDD and resilience. This study includes 4,166 unrelated individuals (Mean age = 56.01, SD = 12.31, n female = 2,634) with complete data of interest.

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Thresholds for MDD Polygenic Risk Scores

Supplementary Table 1. Results of generalized linear mixed models predicting odds ratios for clinical MDD status (SCID), *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion, from five PRS thresholds

| PRS Threshold | Odds Ratio | Lower 95% CI | Upper 95% CI | <i>p</i> value | AIC |
|---------------|------------|--------------|--------------|----------------|---------|
| 0.01 | 1.24 | 1.14 | 1.35 | < 0.001 | 3600.90 |
| 0.05 | 1.25 | 1.15 | 1.37 | < 0.001 | 3598.40 |
| 0.10 | 1.26 | 1.16 | 1.37 | < 0.001 | 3597.50 |
| 0.50 | 1.20 | 1.11 | 1.31 | < 0.001 | 3607.60 |
| 1.00 | 1.20 | 1.10 | 1.31 | < 0.001 | 3608.20 |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score
 NB. Each model was adjusted for baseline age (t_1 : when the SCID was administered), sex and four principal components which control for population stratification

Supplementary Table 2. Results of generalized linear mixed models predicting odds ratios of self-reported MDD status (CIDI-SF), *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion, from five PRS thresholds

| PRS Threshold | Odds Ratio | Lower 95% CI | Upper 95% CI | <i>p</i> value | AIC |
|---------------|------------|--------------|--------------|----------------|---------|
| 0.01 | 1.13 | 1.05 | 1.21 | 0.001 | 4642.80 |
| 0.05 | 1.14 | 1.06 | 1.22 | < 0.001 | 4640.90 |
| 0.10 | 1.16 | 1.08 | 1.25 | < 0.001 | 4636.00 |
| 0.50 | 1.18 | 1.10 | 1.27 | < 0.001 | 4632.80 |
| 1.00 | 1.18 | 1.10 | 1.27 | < 0.001 | 4633.20 |

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score
 NB. Each model was adjusted for age at follow-up (t_2 : when the CIDI-SF was completed), sex and four principal components which control for population stratification

Supplementary Table 3. Correlation Matrix and Descriptive Statistics

| | BRS ₁ | BRS ₂ | BRS ₃ | BRS ₄ | BRS ₅ | BRS ₆ | Resilience | EPQ ₁ | EPQ ₃ | EPQ ₅ | EPQ ₇ | EPQ ₉ | EPQ ₁₁ | EPQ ₁₃ | EPQ ₁₅ | EPQ ₁₇ | EPQ ₁₉ | EPQ ₂₁ | EPQ ₂₃ | Neuroticism | Mean (SD) | N (%) | |
|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------|------------------|------------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------|-----------|---------------|-----------|
| BRS ₁ | - | | | | | | | | | | | | | | | | | | | | | 3.70 (0.96) | |
| BRS ₂ | .47 | - | | | | | | | | | | | | | | | | | | | | 3.40 (1.04) | |
| BRS ₃ | .68 | .45 | - | | | | | | | | | | | | | | | | | | | 3.49 (1.00) | |
| BRS ₄ | .56 | .63 | .51 | - | | | | | | | | | | | | | | | | | | 3.52 (1.04) | |
| BRS ₅ | .62 | .50 | .63 | .52 | - | | | | | | | | | | | | | | | | | 3.55 (1.01) | |
| BRS ₆ | .60 | .61 | .54 | .69 | .57 | - | | | | | | | | | | | | | | | | 3.64 (1.04) | |
| Resilience | .81 | .77 | .79 | .82 | .80 | .84 | - | | | | | | | | | | | | | | | 3.52 (0.82) | |
| EPQ ₁ | -.26 ** | -.24 ** | -.27 ** | -.24 ** | -.28 ** | -.24 ** | -.32 ** | - | | | | | | | | | | | | | | | 1513 (36) |
| EPQ ₃ | -.30 ** | -.26 ** | -.28 ** | -.26 ** | -.29 ** | -.27 ** | -.34 ** | .63 * | - | | | | | | | | | | | | | | 1310 (31) |
| EPQ ₅ | -.15 ** | -.14 ** | -.14 ** | -.13 ** | -.15 ** | -.14 ** | -.18 ** | .52 * | .36 * | - | | | | | | | | | | | | | 1105 (27) |
| EPQ ₇ | -.22 ** | -.20 ** | -.23 ** | -.23 ** | -.23 ** | -.22 ** | -.27 ** | .40 * | .42 * | .30 * | - | | | | | | | | | | | | 1847 (44) |
| EPQ ₉ | -.30 ** | -.27 ** | -.27 ** | -.26 ** | -.27 ** | -.27 ** | -.34 ** | .70 * | .66 * | .47 * | .45 * | - | | | | | | | | | | | 1276 (31) |
| EPQ ₁₁ | -.24 ** | -.24 ** | -.23 ** | -.23 ** | -.24 ** | -.24 ** | -.30 ** | .43 * | .40 * | .36 * | .47 * | .40 * | - | | | | | | | | | | 990 (24) |
| EPQ ₁₃ | -.27 ** | -.27 ** | -.27 ** | -.27 ** | -.30 ** | -.25 ** | -.34 ** | .50 * | .47 * | .39 * | .57 * | .49 * | .58 * | - | | | | | | | | | 2382 (57) |
| EPQ ₁₅ | -.23 ** | -.22 ** | -.20 ** | -.20 ** | -.20 ** | -.20 ** | -.26 ** | .52 * | .43 * | .50 * | .47 * | .44 * | .69 * | .66 * | - | | | | | | | | 653 (16) |
| EPQ ₁₇ | -.23 ** | -.20 ** | -.21 ** | -.22 ** | -.24 ** | -.20 ** | -.27 ** | .40 * | .42 * | .28 * | .60 * | .43 * | .50 * | .62 * | .46 * | - | | | | | | | 1796 (43) |
| EPQ ₁₉ | -.23 ** | -.24 ** | -.22 ** | -.22 ** | -.24 ** | -.23 ** | -.29 ** | .47 * | .43 * | .38 * | .41 * | .46 * | .75 * | .61 * | .70 * | .43 * | - | | | | | | 848 (20) |
| EPQ ₂₁ | -.22 ** | -.18 ** | -.19 ** | -.18 ** | -.20 ** | -.21 ** | -.25 ** | .57 * | .55 * | .36 * | .44 * | .67 * | .38 * | .42 * | .45 * | .40 * | .43 * | - | | | | | 582 (14) |
| EPQ ₂₃ | -.24 ** | -.20 ** | -.24 ** | -.23 ** | -.23 ** | -.21 ** | -.28 ** | .49 * | .50 * | .34 * | .51 * | .48 * | .48 * | .59 * | .49 * | .66 * | .48 * | .49 * | - | | | | 1107 (27) |
| Neuroticism | -.41 | -.37 | -.39 | -.38 | -.40 | -.38 | -.48 | .64 ** | .60 ** | .49 ** | .59 ** | .64 ** | .60 ** | .64 ** | .58 ** | .61 ** | .59 ** | .51 ** | .61 ** | - | | 3.70 (3.17) | |
| Aget1 | .04 | .04 | .04 | .03 | .04 | .05 | .05 | -.15 ** | -.13 ** | -.14 ** | -.04 ** | -.14 ** | -.06 ** | -.04 ** | -.04 ** | -.06 ** | -.12 ** | -.02 ** | -.05 ** | -.14 | | 50.28 (12.34) | |
| Aget2 | .05 | .04 | .04 | .03 | .04 | .05 | .05 | -.15 ** | -.13 ** | -.13 ** | -.03 ** | -.13 ** | -.06 ** | -.04 ** | -.04 * | -.06 ** | -.12 ** | -.01 ** | -.04 ** | -.14 | | 56.01 (12.31) | |
| Sex (F) | -.10 ** | -.06 ** | -.09 ** | -.09 ** | -.11 ** | -.06 ** | -.10 ** | .10 * | .22 * | -.06 * | .37 * | .06 * | .16 * | .26 * | .15 * | .27 * | .04 * | .20 * | .26 * | .17 ** | | 2634 (63) | |
| SCID | -.27 ** | -.23 ** | -.24 ** | -.23 ** | -.28 ** | -.24 ** | -.31 ** | .45 * | .51 * | .22 * | .33 * | .43 * | .37 * | .39 * | .38 * | .32 * | .41 * | .47 * | .42 * | .36 ** | | 664 (16) | |
| CIDI-SF | -.31 ** | -.26 ** | -.29 ** | -.26 ** | -.31 ** | -.28 ** | -.35 ** | .35 * | .42 * | .16 * | .22 * | .37 * | .26 * | .26 * | .26 * | .24 * | .29 * | .39 * | .33 * | .29 ** | | 1068 (26) | |

Abbreviations: Age₁, Age at baseline; Age₂, Age at re-contact; BRS, Individual items from the Brief Resilience Scale; Resilience, Total score from the Brief Resilience Scale; EPQ, Individual items from the Eysenck Personality Questionnaire Short-Form; Neuroticism, Total score from the Eysenck Personality Questionnaire Short-Form; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form representing self-reported MDD. N.B. All p-values significant at p ≤ 0.01. EPQ items represent the number and percentage of ‘Yes’ responses. SCID and CIDI-SF represent the number and percentage of individuals meeting criteria for clinical and self-reported MDD, respectively. All coefficients represent Pearson correlations except those denoted by * which represent tetrachoric correlations – resultant from both variables being binary, and those denoted by ** which represent point biserial correlations – resultant from binary and continuous variables

Descriptive Statistics for Clinical and Self-reported MDD

Clinical MDD

Based on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First *et al.*, 1997) at baseline assessment (2006-2011), clinically diagnosed MDD cases were predominately female (73%) and younger than non-MDD cases (61% female, $M = 49.13$, $SD = 11.39$ and $M = 50.49$, $SD = 12.50$, respectively); ($t(990.30) = 2.78$, $p < 0.001$, Cohen's $d = .11$). Clinical MDD cases were found to have significantly higher neuroticism scores ($M = 6.31$, $SD = 3.28$) than did non-MDD cases ($M = 3.20$, $SD = 2.90$); ($t(869.91) = 22.75$, $p < 0.001$, Cohen's $d = 1.00$). Clinically diagnosed MDD cases were found to score significantly lower in resilience ($M = 2.94$, $SD = 0.85$) in comparison to non-MDD cases ($M = 3.63$, $SD = 0.76$); ($t(879.19) = 19.48$, $p < 0.001$, Cohen's $d = .08$).

Self-reported MDD

Using the Composite International Diagnostic Interview – Short Form (CIDI-SF; Kessler *et al.*, 1998) at re-contact (2014-2017), a larger proportion of females met criteria for self-reported depression (75%) in comparison to non-MDD cases (59%). Self-reported MDD cases were younger ($M = 54.40$, $SD = 12.28$) in comparison to non-MDD cases ($M = 56.56$, $SD = 12.27$) at re-contact; ($t(1852.70) = 4.96$, $p < 0.001$, Cohen's $d = .18$). Individuals self-reporting MDD scored higher in neuroticism than did non-MDD cases ($M = 5.26$, $SD = 3.45$ and $M = 3.16$, $SD = 2.88$, respectively); ($t(1608) = 17.80$, $p < 0.001$, Cohen's $d = .66$). Significant group differences were found between self-reported MDD cases ($M = 3.03$, $SD = 0.86$) and non-MDD cases ($M = 3.69$, $SD = 0.73$) in resilience; ($t(1617.60) = 22.33$, $p < 0.001$, Cohen's $d = .83$), whereby self-reported MDD cases scored lower on psychological resilience.

Overlap between clinical and self-reported MDD

The two measures of MDD were taken at two separate time-points using two different methods, approximately six years apart. Below is a table detailing the overlap between these two measures in our sample of 4,166 individuals.

Supplementary Table 4

Table demonstrating the overlap of individuals meeting criteria for clinical and self-reported MDD in the current sample ($n = 4,166$)

| | | Self-reported MDD (CIDI-SF) | |
|---------------------|-----------------------|-----------------------------|-----------------------|
| | | Met criteria | Did not meet criteria |
| Clinical MDD (SCID) | Met criteria | 411 | 253 |
| | Did not meet criteria | 6157 | 2,845 |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder

References

- First, M., Spitzer, R., Gibbon, M. & Williams, J. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). American Psychiatric Publishing, Inc.: Washington, DC, USA.
- Kessler, R., Andrews, G., Mroczek, D., Ustun, B. & Wittchen, H.-U. (1998). The World Health Organisation Composite International Diagnostic Interview short-form (CIDI-SF). pp. 171-185. International Journal of Methods in Psychiatric Research.

Moderation models for clinical MDD

Supplementary Table 5. Results of a generalised linear model predicting odds ratios for clinical MDD status, *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion

| MDD Outcome | Variables | Odds ratio | Lower 95% CIs | Upper 95% CIs | <i>p</i> value | AIC |
|-------------------|-----------------------|----------------------|-----------------------|--------------------------|--------------------------|---------|
| SCID | Age _{t1} | 0.99 | 0.99 | 1.00 | 0.031 | 3607.60 |
| | Sex (F) | 1.71 | 1.42 | 2.07 | 1.53x10 ⁻⁸ | |
| | PRS | 1.20 | 1.11 | 1.31 | 1.87x10 ⁻⁵ | |
| | C1 | 2.92 | 0.00 | 7.89x10 ²⁴ | 0.969 | |
| | C2 | 0.01 | 0.00 | 8.63x10 ²⁶ | 0.886 | |
| | C3 | 0.00 | 0.00 | 1.05 | 0.127 | |
| | C4 | 1.83x10 ⁴ | 0.01 | 2.07x10 ¹⁰ | 0.169 | |
| | Age _{t1} | 0.99 | 0.99 | 1.00 | 0.026 | |
| Sex (F) | 1.33 | 1.09 | 1.63 | 0.005 | | |
| PRS | 1.16 | 1.05 | 1.29 | 0.004 | | |
| Neuroticism | 2.49 | 2.28 | 2.72 | < 2.00x10 ⁻¹⁶ | | |
| PRS * Neuroticism | 0.92 | 0.84 | 1.00 | 0.062 | | |
| C1 | 1.60x10 ³ | 0.00 | 2.18x10 ²⁹ | 0.805 | | |
| C2 | 0.00 | 0.00 | 2.05x10 ²⁶ | 0.431 | | |
| C3 | 0.01 | 0.00 | 8.08x10 ² | 0.516 | | |
| C4 | 134.63 | 0.00 | 3.43x10 ⁸ | 0.062 | | |
| SCID | Age _{t1} | 0.99 | 0.99 | 1.00 | 0.030 | 3251.90 |
| | Sex (F) | 1.53 | 1.26 | 1.86 | 1.97x10 ⁻⁵ | |
| | PRS | 1.17 | 1.06 | 1.30 | 0.002 | |
| | Resilience | 0.44 | 0.40 | 0.48 | < 2.00x10 ⁻¹⁶ | |
| | PRS * Resilience | 1.06 | 0.97 | 1.16 | 0.211 | |
| | C1 | 0.00 | 0.00 | 1.58x10 ²² | 0.753 | |
| | C2 | 0.00 | 0.00 | 8.81x10 ²² | 0.629 | |
| | C3 | 0.00 | 0.00 | 2.42x10 ² | 0.323 | |
| C4 | 1.03x10 ⁴⁸ | 0.04 | 2.44x10 ¹¹ | 0.124 | | |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score; Age_{t1}, Age at the time of baseline; C1-4, the principal components which control for population stratification

N.B. Neuroticism has been controlled for Age_{t1} and these residuals used within the model. Resilience has been controlled for Age_{t2} before entering the model. Threshold for PRS = 0.50

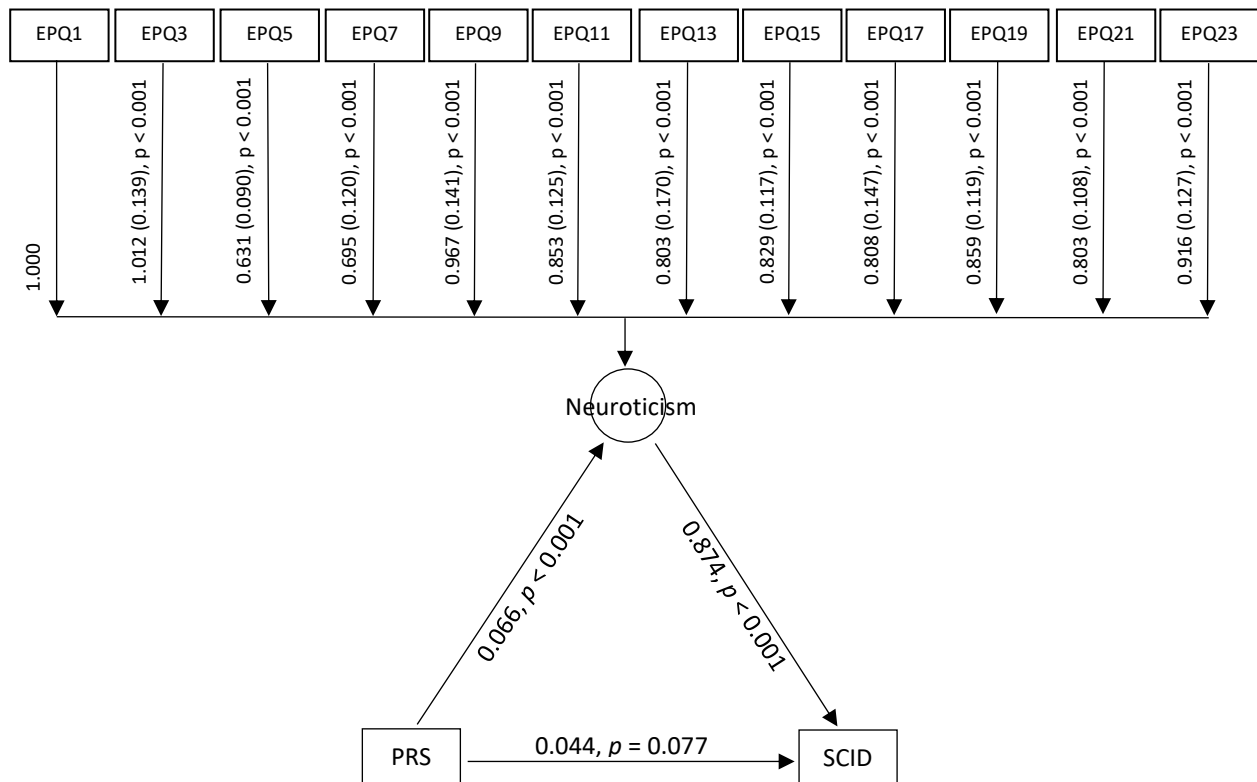
Moderation models for self-reported MDD

Supplementary Table 6. Results of a generalised linear model predicting odds ratios for self-reported MDD status, *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion

| MDD Outcome | Variables | Odds ratio | Lower 95% CIs | Upper 95% CIs | <i>p</i> value | AIC |
|-------------|-------------------|-----------------------|---------------|-----------------------|--------------------------|---------|
| CIDI-SF | Age _{t2} | 0.99 | 0.98 | 0.99 | 1.88x10 ⁻⁵ | 4632.80 |
| | Sex (F) | 1.94 | 1.66 | 2.28 | < 2.00x10 ⁻¹⁶ | |
| | PRS | 1.18 | 1.10 | 1.27 | 6.01x10 ⁻⁶ | |
| | C1 | 5.87x10 ¹⁸ | 0.01 | 2.18x10 ⁴⁰ | 0.082 | |
| | C2 | 0.63 | 0.00 | 3.17x10 ²⁴ | 0.987 | |
| | C3 | 0.00 | 0.00 | 1.85 | 0.068 | |
| | C4 | 5.41x10 ² | 0.00 | 7.40x10 ⁷ | 0.298 | |
| CIDI-SF | Age _{t2} | 0.99 | 0.98 | 0.99 | 4.48x10 ⁻⁶ | 4366.40 |
| | Sex (F) | 1.66 | 1.41 | 1.95 | 1.03x10 ⁻⁹ | |
| | PRS | 1.13 | 1.05 | 1.22 | 0.002 | |
| | Neuroticism | 1.81 | 1.68 | 1.95 | < 2.00x10 ⁻¹⁶ | |
| | PRS * Neuroticism | 0.97 | 0.90 | 1.04 | 0.416 | |
| | C1 | 1.81x10 ²¹ | 0.54 | 4.30x10 ⁴³ | 0.058 | |
| | C2 | 0.07 | 0.00 | 3.19x10 ²⁴ | 0.931 | |
| CIDI-SF | Age _{t2} | 0.99 | 0.98 | 0.99 | 4.15x10 ⁻⁶ | 4156.80 |
| | Sex (F) | 1.80 | 1.52 | 2.12 | 4.38x10 ⁻¹² | |
| | PRS | 1.14 | 1.06 | 1.24 | 0.001 | |
| | Resilience | 0.43 | 0.40 | 0.47 | < 2.00x10 ⁻¹⁶ | |
| | PRS * Resilience | 1.07 | 0.99 | 1.17 | 0.080 | |
| | C1 | 3.75x10 ¹⁷ | 0.00 | 1.06x10 ⁴¹ | 0.134 | |
| | C2 | 0.00 | 0.00 | 4.61x10 ²¹ | 0.733 | |
| CIDI-SF | C3 | 0.00 | 0.00 | 16.60 | 0.168 | |
| | C4 | 1.28x10 ³ | 0.00 | 1.17 | 0.266 | |

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score; Age_{t2}, Age at the time of re-contact; C1-4, the principal components which control for population stratification

N.B. Neuroticism has been controlled for Age_{t1} and these residuals used within the model. Resilience has been controlled for Age_{t2}, before entering the model. Threshold for PRS = 0.50



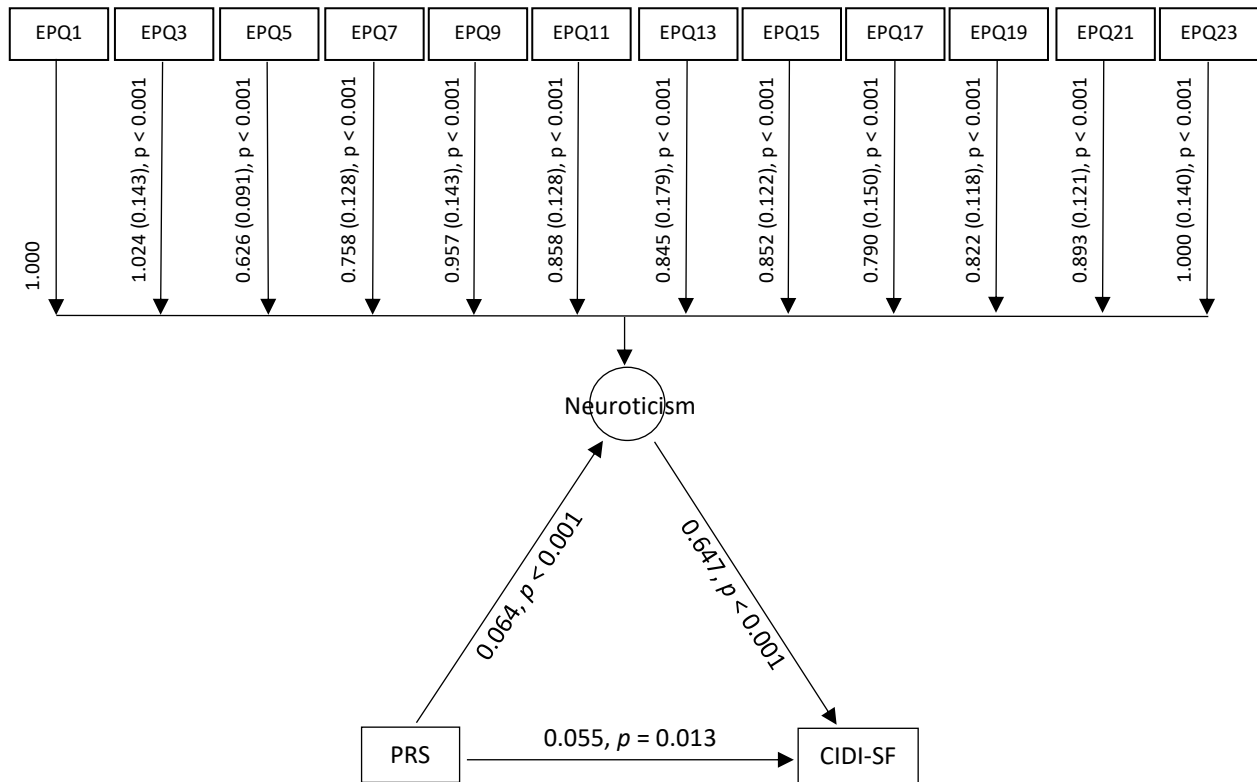
Supplementary Figure 1. Path diagram of **Model 1A**, which includes factor loadings onto the latent variable neuroticism, a direct path between PRS and clinical MDD status, and indirect path through neuroticism. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; EPQ; the Eysenck Personality Questionnaire Short Form-Revised

Supplementary Table 7. Results of all standardised path coefficients from **Model 1A** examining the mediation of Neuroticism through PRS to clinical MDD status

| Model description | | β | S.E | <i>p</i> value |
|-------------------|-------------------|---------|-------|----------------|
| SCID ~ | PRS | 0.044 | 0.025 | 0.077 |
| SCID ~ | Neuroticism | 0.874 | 0.114 | < 0.001 |
| SCID ~ | Sex | 0.191 | 0.054 | < 0.001 |
| SCID ~ | Age _{t1} | 0.003 | 0.027 | 0.900 |
| SCID ~ | C1 | 0.004 | 0.024 | 0.856 |
| SCID ~ | C2 | -0.004 | 0.025 | 0.868 |
| SCID ~ | C3 | -0.020 | 0.025 | 0.429 |
| SCID ~ | C4 | 0.013 | 0.025 | 0.605 |
| Neuroticism ~ | PRS | 0.066 | 0.010 | < 0.001 |
| Neuroticism ~ | Sex | 0.116 | 0.019 | < 0.001 |
| Neuroticism ~ | Age _{t1} | -0.063 | 0.010 | < 0.001 |
| Neuroticism ~ | C1 | -0.004 | 0.005 | 0.514 |
| Neuroticism ~ | C2 | 0.001 | 0.005 | 0.828 |
| Neuroticism ~ | C3 | -0.020 | 0.006 | 0.001 |
| Neuroticism ~ | C4 | 0.022 | 0.006 | < 0.001 |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; C1-4, the principal components which control for population stratification



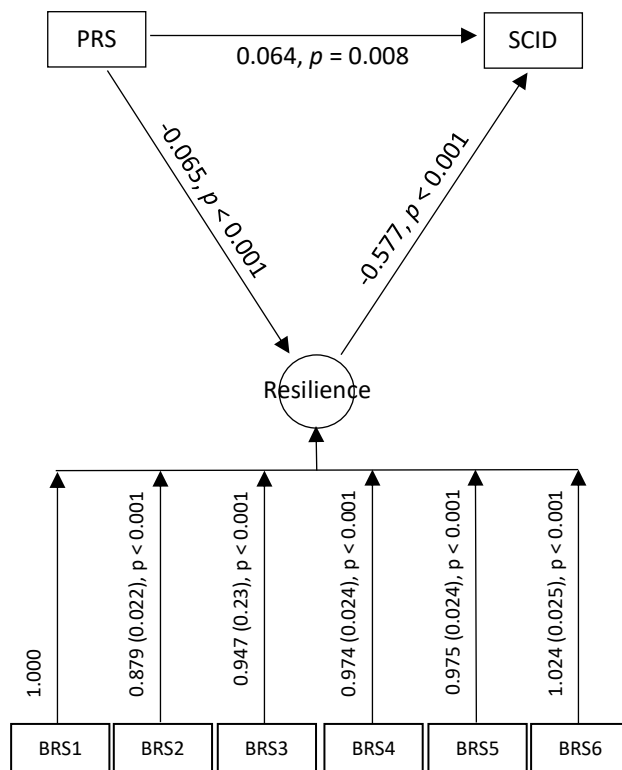
Supplementary Figure 2. Path diagram of **Model 2A**, which includes factor loadings onto the latent variable neuroticism, a direct path between PRS and self-reported MDD status, and indirect path through neuroticism. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; EPQ; the Eysenck Personality Questionnaire Short Form-Revised

Supplementary Table 8. Results of all standardised path coefficients from **Model 2A** examining the mediation of Neuroticism through PRS to self-reported MDD status

| Model description | | β | S.E | <i>p</i> value |
|-------------------|-------------------|---------|-------|----------------|
| CIDI-SF ~ | PRS | 0.055 | 0.022 | 0.013 |
| CIDI-SF ~ | Neuroticism | 0.647 | 0.087 | < 0.001 |
| CIDI-SF ~ | Sex | 0.312 | 0.047 | < 0.001 |
| CIDI-SF ~ | Age _{t2} | -0.030 | 0.188 | 0.874 |
| CIDI-SF ~ | C1 | 0.045 | 0.024 | 0.065 |
| CIDI-SF ~ | C2 | -0.002 | 0.022 | 0.931 |
| CIDI-SF ~ | C3 | -0.028 | 0.022 | 0.203 |
| CIDI-SF ~ | C4 | 0.008 | 0.022 | 0.705 |
| Neuroticism ~ | PRS | 0.064 | 0.010 | < 0.001 |
| Neuroticism ~ | Sex | 0.119 | 0.020 | < 0.001 |
| Neuroticism ~ | Age _{t1} | -0.249 | 0.055 | < 0.001 |
| Neuroticism ~ | C1 | -0.003 | 0.005 | 0.540 |
| Neuroticism ~ | C2 | 0.002 | 0.005 | 0.719 |
| Neuroticism ~ | C3 | -0.020 | 0.006 | 0.001 |
| Neuroticism ~ | C4 | 0.021 | 0.006 | 0.001 |

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification



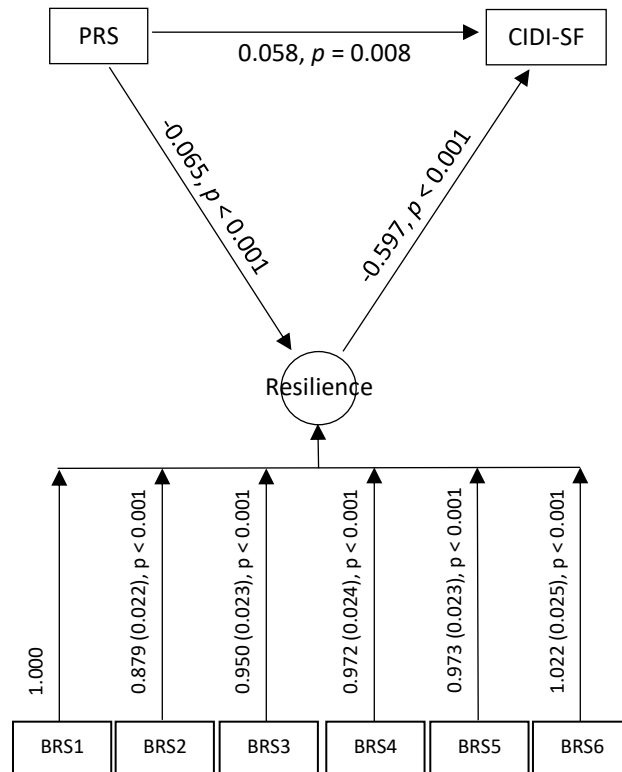
Supplementary Figure 3. Path diagram of **Model 1B**, which includes factor loadings onto the latent variable resilience, a direct path between PRS and clinical MDD status, and indirect path through resilience. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; BRS; the Brief Resilience Scale

Supplementary Table 9. Results of all standardised path coefficients from **Model 1B** examining the mediation of Resilience through PRS to clinical MDD status

| Model description | | β | S.E | <i>p</i> value |
|-------------------|-------------------|---------|-------|----------------|
| SCID ~ | PRS | 0.064 | 0.024 | 0.008 |
| SCID ~ | Resilience | -0.577 | 0.018 | < 0.001 |
| SCID ~ | Sex | 0.197 | 0.052 | < 0.001 |
| SCID ~ | Age _{t1} | -0.452 | 0.201 | 0.024 |
| SCID ~ | C1 | -0.008 | 0.024 | 0.741 |
| SCID ~ | C2 | -0.010 | 0.025 | 0.697 |
| SCID ~ | C3 | -0.028 | 0.025 | 0.271 |
| SCID ~ | C4 | 0.030 | 0.025 | 0.228 |
| Resilience ~ | PRS | -0.577 | 0.018 | < 0.001 |
| Resilience ~ | Sex | -0.165 | 0.014 | < 0.001 |
| Resilience ~ | Age _{t2} | 0.010 | 0.056 | 0.860 |
| Resilience ~ | C1 | -0.015 | 0.007 | 0.021 |
| Resilience ~ | C2 | -0.014 | 0.007 | 0.040 |
| Resilience ~ | C3 | 0.018 | 0.007 | 0.006 |
| Resilience ~ | C4 | -0.004 | 0.007 | 0.531 |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification

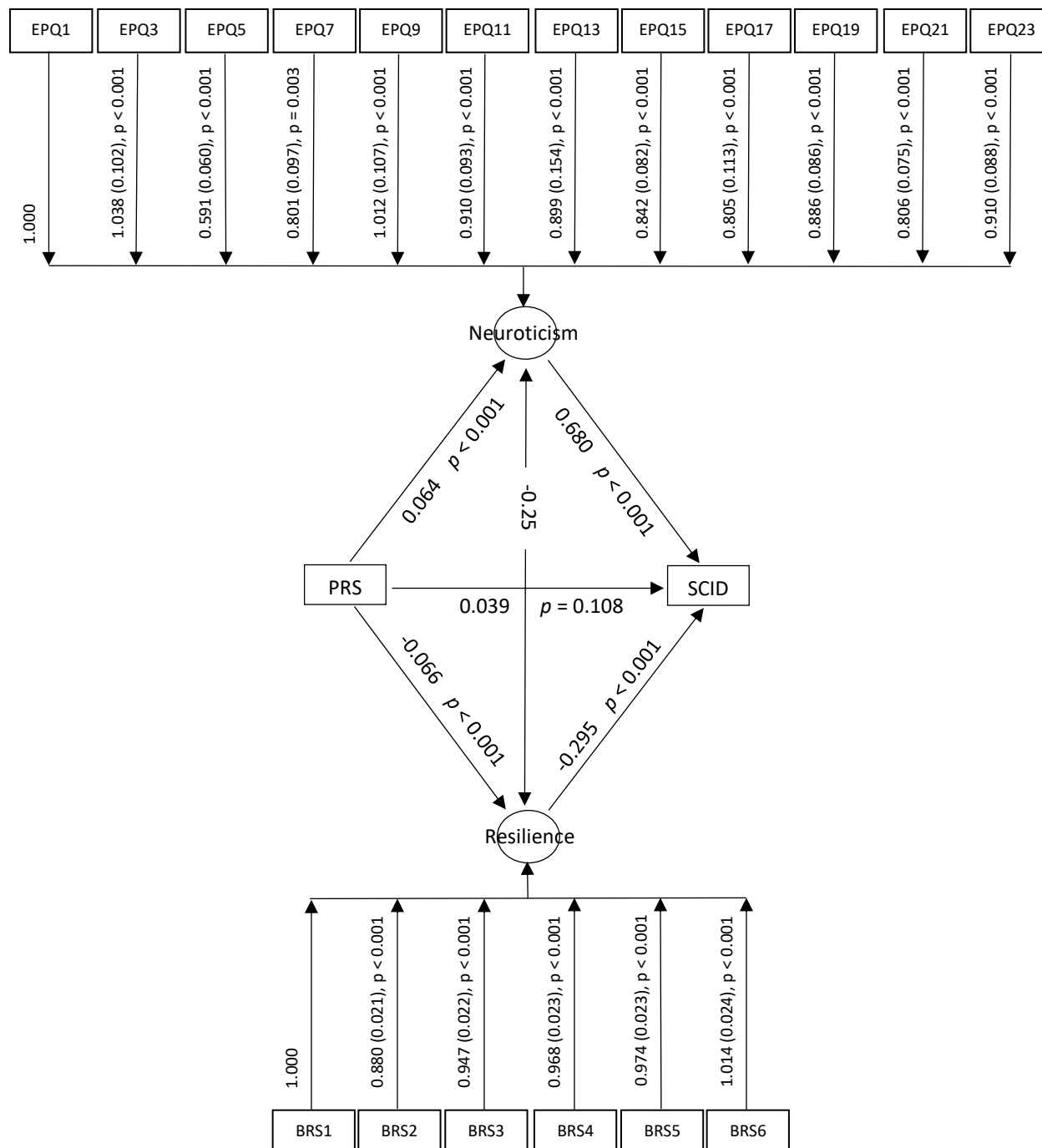


Supplementary Figure 4. Path diagram of **Model 2B**, which includes factor loadings onto the latent variable resilience, a direct path between PRS and self-reported MDD status, and indirect path through resilience. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured. Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; BRS; the Brief Resilience Scale

Supplementary Table 10. Results of all standardised path coefficients from **Model 2B** examining the mediation of Resilience through PRS to self-reported MDD status

| Model description | β | S.E | p value |
|--------------------------------|---------|-------|-----------|
| CIDI-SF ~ PRS | 0.058 | 0.022 | 0.008 |
| CIDI-SF ~ Resilience | -0.597 | 0.018 | < 0.001 |
| CIDI-SF ~ Sex | 0.290 | 0.047 | < 0.001 |
| CIDI-SF ~ Age _{t2} | -0.070 | 0.022 | 0.001 |
| CIDI-SF ~ C1 | 0.033 | 0.024 | 0.171 |
| CIDI-SF ~ C2 | -0.009 | 0.022 | 0.683 |
| CIDI-SF ~ C3 | -0.030 | 0.022 | 0.177 |
| CIDI-SF ~ C4 | 0.019 | 0.022 | 0.383 |
| Resilience ~ PRS | -0.065 | 0.007 | < 0.001 |
| Resilience ~ Sex | -0.165 | 0.014 | < 0.001 |
| Resilience ~ Age _{t2} | 0.037 | 0.006 | < 0.001 |
| Resilience ~ C1 | -0.015 | 0.007 | 0.021 |
| Resilience ~ C2 | -0.014 | 0.007 | 0.040 |
| Resilience ~ C3 | 0.018 | 0.007 | 0.006 |
| Resilience ~ C4 | -0.004 | 0.007 | 0.531 |

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification



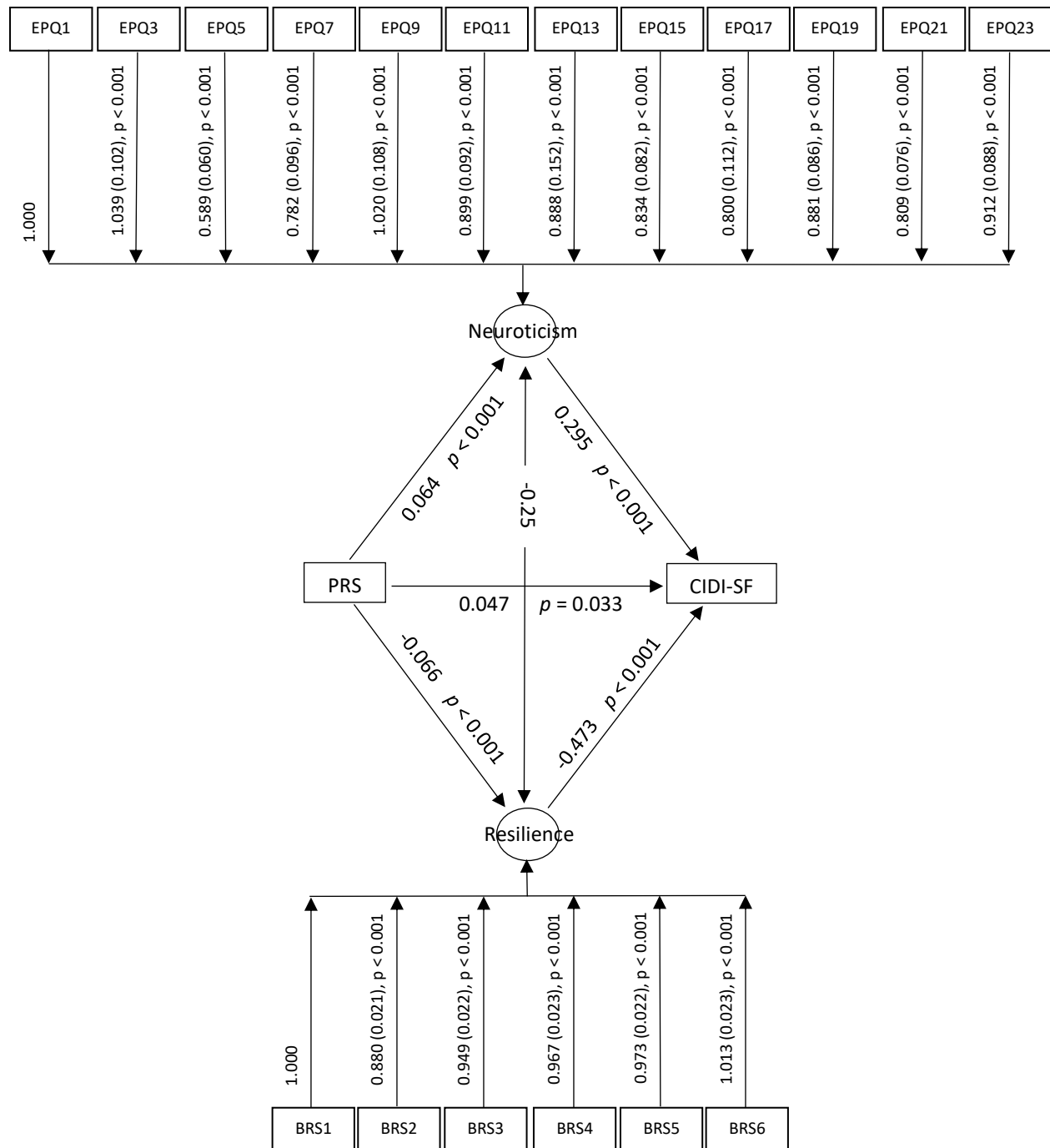
Supplementary Figure 5. Path diagram of **Model 1C**, which includes factor loadings onto the latent variables neuroticism and resilience, a direct bath between PRS and clinical MDD status, an indirect path through neuroticism and an indirect path through resilience. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; EPQ, the Eysenck Personality Questionnaire Short Form-Revised; BRS, the Brief Resilience Scale

Supplementary Table 11. Results of all standardised path coefficients from **Model 1C** examining the separate mediation of Neuroticism and Resilience through PRS to clinical MDD status

| Model description | | β | S.E | p value |
|-------------------|-------------------|---------|-------|-----------|
| SCID ~ | PRS | 0.039 | 0.024 | 0.108 |
| SCID ~ | Neuroticism | 0.680 | 0.105 | < 0.001 |
| SCID ~ | Resilience | -0.295 | 0.044 | < 0.001 |
| SCID ~ | Sex | 0.164 | 0.053 | 0.002 |
| SCID ~ | Age _{t1} | -0.283 | 0.205 | 0.166 |
| SCID ~ | C1 | -0.001 | 0.024 | 0.962 |
| SCID ~ | C2 | -0.007 | 0.025 | 0.784 |
| SCID ~ | C3 | -0.019 | 0.025 | 0.440 |
| SCID ~ | C4 | 0.017 | 0.025 | 0.499 |
| Neuroticism ~ | PRS | 0.064 | 0.008 | < 0.001 |
| Neuroticism ~ | Sex | 0.116 | 0.017 | < 0.001 |
| Neuroticism ~ | Age _{t1} | -0.249 | 0.052 | < 0.001 |
| Neuroticism ~ | C1 | -0.003 | 0.005 | 0.511 |
| Neuroticism ~ | C2 | 0.001 | 0.005 | 0.782 |
| Neuroticism ~ | C3 | -0.020 | 0.006 | < 0.001 |
| Neuroticism ~ | C4 | 0.021 | 0.006 | < 0.001 |
| Resilience ~ | PRS | -0.066 | 0.007 | < 0.001 |
| Resilience ~ | Sex | -0.165 | 0.014 | < 0.001 |
| Resilience ~ | Age _{t2} | 0.019 | 0.057 | 0.733 |
| Resilience ~ | C1 | -0.016 | 0.007 | 0.021 |
| Resilience ~ | C2 | -0.014 | 0.007 | 0.040 |
| Resilience ~ | C3 | 0.018 | 0.007 | 0.006 |
| Resilience ~ | C4 | -0.004 | 0.007 | 0.530 |

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification



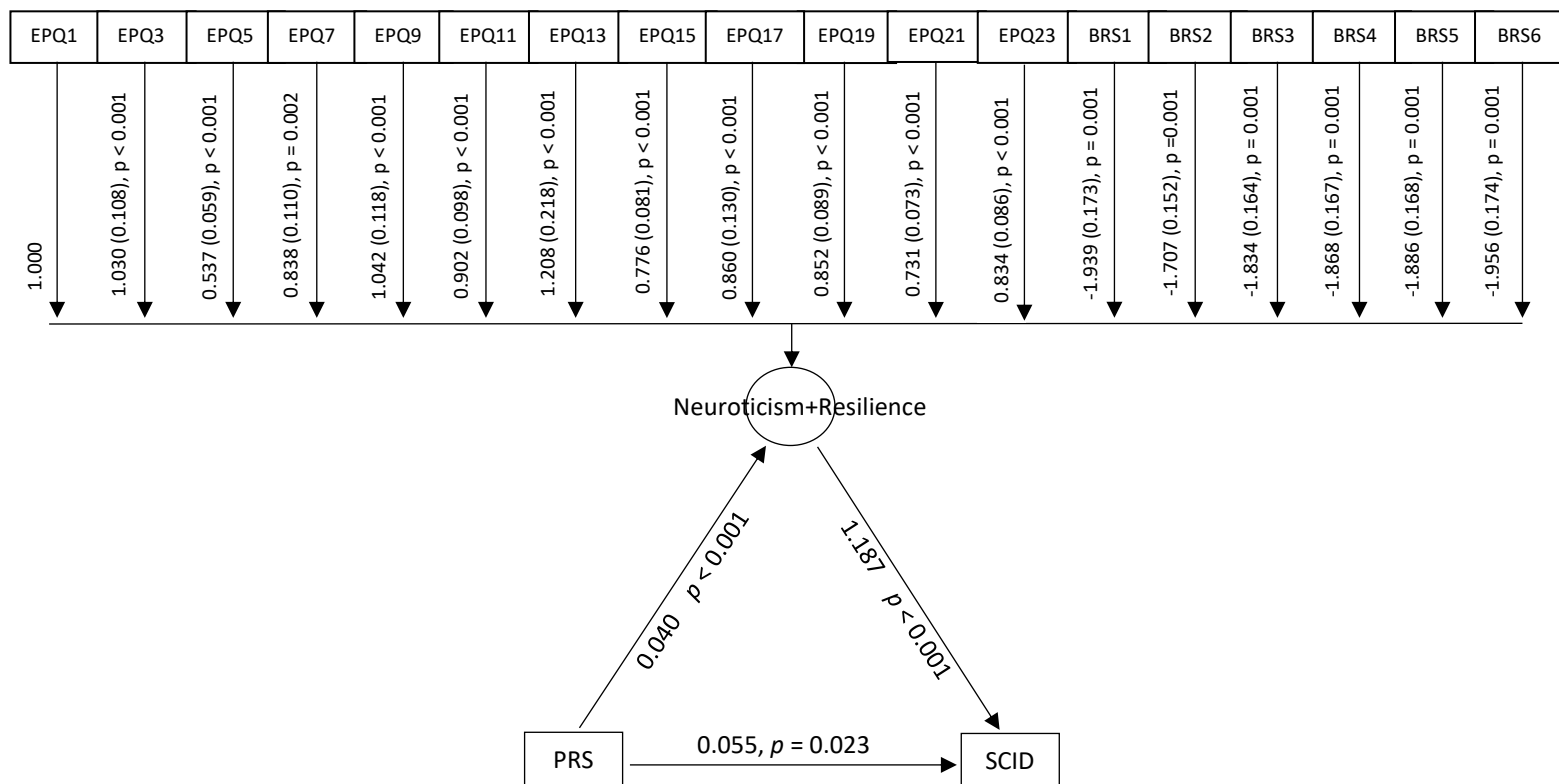
Supplementary Figure 6. Path diagram of **Model 2C**, which includes factor loadings onto the latent variables neuroticism and resilience, a direct bath between PRS and self-reported MDD status, an indirect path through neuroticism and an indirect path through resilience. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; EPQ, the Eysenck Personality Questionnaire Short Form-Revised; BRS, the Brief Resilience Scale

Supplementary Table 12. Results of all standardised path coefficients from **Model 2C** examining the separate mediation of Neuroticism and Resilience through PRS to self-reported MDD status

| Model description | | β | S.E | p value |
|-------------------|-------------------|---------|-------|-----------|
| CIDI-SF ~ | PRS | 0.047 | 0.022 | 0.033 |
| CIDI-SF ~ | Neuroticism | 0.295 | 0.070 | < 0.001 |
| CIDI-SF ~ | Resilience | -0.473 | 0.035 | < 0.001 |
| CIDI-SF ~ | Sex | 0.276 | 0.047 | < 0.001 |
| CIDI-SF ~ | Age _{t2} | -0.016 | 0.190 | 0.933 |
| CIDI-SF ~ | C1 | 0.036 | 0.024 | 0.136 |
| CIDI-SF ~ | C2 | -0.008 | 0.022 | 0.730 |
| CIDI-SF ~ | C3 | -0.027 | 0.022 | 0.231 |
| CIDI-SF ~ | C4 | 0.013 | 0.022 | 0.537 |
| Neuroticism ~ | PRS | 0.064 | 0.008 | < 0.001 |
| Neuroticism ~ | Sex | 0.116 | 0.017 | < 0.001 |
| Neuroticism ~ | Age _{t1} | -0.249 | 0.052 | < 0.001 |
| Neuroticism ~ | C1 | -0.003 | 0.005 | 0.513 |
| Neuroticism ~ | C2 | 0.001 | 0.005 | 0.783 |
| Neuroticism ~ | C3 | -0.020 | 0.006 | < 0.001 |
| Neuroticism ~ | C4 | 0.021 | 0.006 | < 0.001 |
| Resilience ~ | PRS | -0.066 | 0.007 | < 0.001 |
| Resilience ~ | Sex | -0.166 | 0.014 | < 0.001 |
| Resilience ~ | Age _{t2} | 0.029 | 0.057 | 0.608 |
| Resilience ~ | C1 | -0.016 | 0.007 | 0.021 |
| Resilience ~ | C2 | -0.014 | 0.007 | 0.040 |
| Resilience ~ | C3 | 0.018 | 0.007 | 0.006 |
| Resilience ~ | C4 | -0.004 | 0.007 | 0.530 |

Abbreviations: Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification



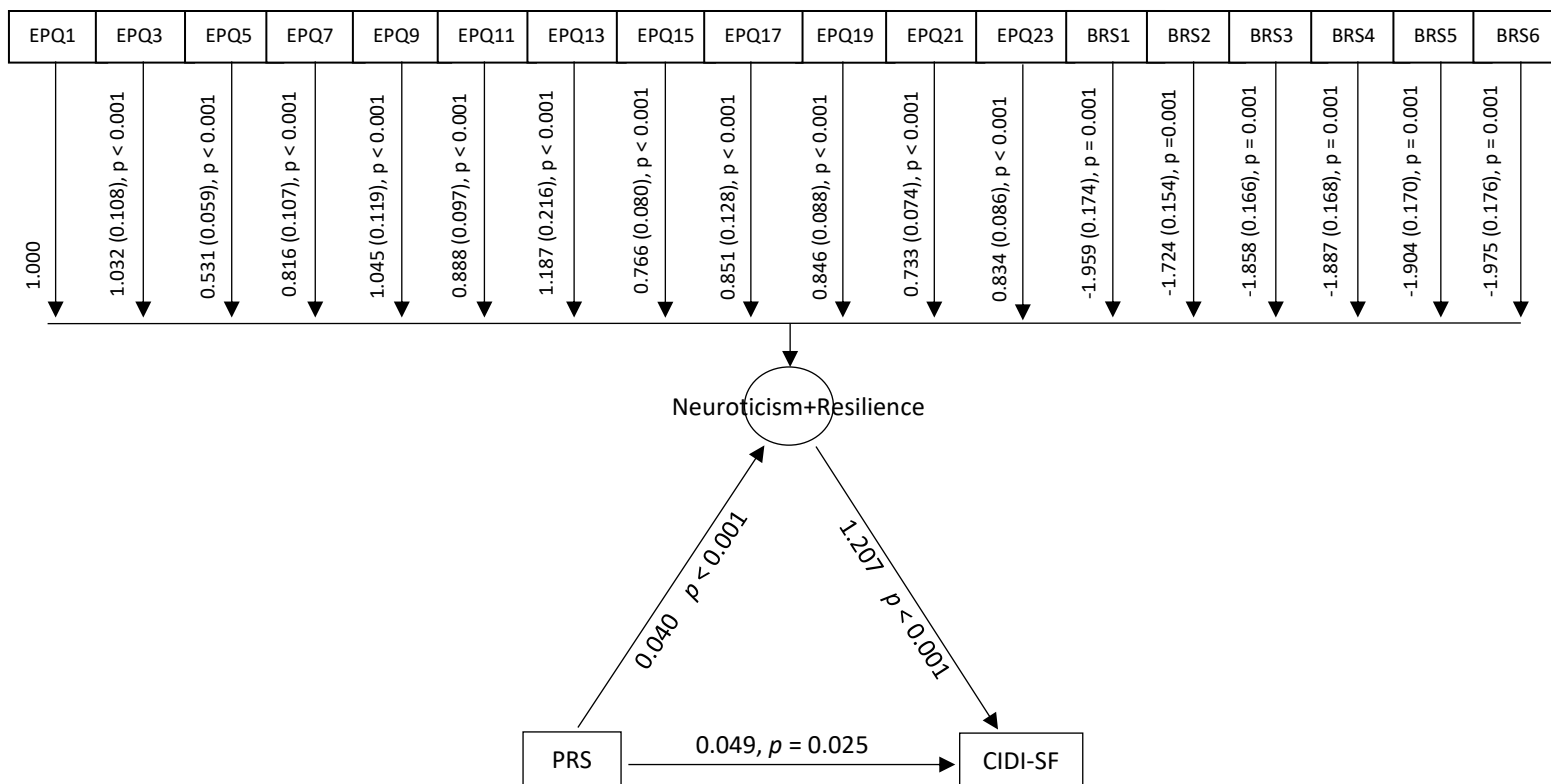
Supplementary Figure 7. Path diagram of **Model 1D**, which includes factor loadings onto the latent variable Neuroticism+Resilience, a direct path between PRS and clinical MDD status, and an indirect path through the latent variable (Neuroticism+Resilience). Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale.

Supplementary Table 13. Results of all standardised path coefficients from **Model 1D** examining the mediation of a latent variable Neuroticism+Resilience through PRS to clinical MDD status

| Model description | β | S.E | p value |
|--|---------|-------|---------|
| SCID ~ PRS | 0.055 | 0.024 | 0.023 |
| SCID ~ Neuroticism+Resilience | 1.187 | 0.108 | < 0.001 |
| SCID ~ Sex | 0.184 | 0.052 | < 0.001 |
| SCID ~ Age _{t1} | -0.371 | 0.203 | 0.067 |
| SCID ~ C1 | -0.004 | 0.024 | 0.856 |
| SCID ~ C2 | -0.008 | 0.025 | 0.748 |
| SCID ~ C3 | -0.024 | 0.025 | 0.341 |
| SCID ~ C4 | 0.023 | 0.024 | 0.351 |
| Neuroticism+Resilience ~ PRS | 0.040 | 0.005 | < 0.001 |
| Neuroticism+Resilience ~ Sex | 0.091 | 0.010 | < 0.001 |
| Neuroticism+Resilience ~ Age _{t1} | -0.068 | 0.026 | 0.008 |
| Neuroticism+Resilience ~ Age _{t2} | 0.042 | 0.025 | 0.093 |
| Neuroticism+Resilience ~ C1 | 0.005 | 0.003 | 0.120 |
| Neuroticism+Resilience ~ C2 | 0.005 | 0.003 | 0.073 |
| Neuroticism+Resilience ~ C3 | -0.012 | 0.003 | < 0.001 |
| Neuroticism+Resilience ~ C4 | 0.008 | 0.003 | 0.009 |

Abbreviations: Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD ; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale.



Supplementary Figure 12. Path diagram of **Model 2D**, which includes factor loadings onto the latent variable Neuroticism+Resilience, a direct path between PRS and self-reported MDD status, and an indirect path through the latent variable (Neuroticism+Resilience). Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.

Abbreviations: PRS, Polygenic Risk Score; Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale.

Supplementary Table 14. Results of all standardised path coefficients from **Model 2D** examining the mediation of a latent variable Neuroticism+Resilience through PRS to self-reported MDD status

| Model description | | β | S.E | p value |
|--------------------------|------------------------|---------|-------|-----------|
| CIDI-SF ~ | PRS | 0.049 | 0.022 | 0.025 |
| CIDI-SF ~ | Neuroticism+Resilience | 1.207 | 0.109 | < 0.001 |
| CIDI-SF ~ | Sex | 0.280 | 0.047 | < 0.001 |
| CIDI-SF ~ | Age _{t2} | -0.071 | 0.190 | 0.708 |
| CIDI-SF ~ | C1 | 0.037 | 0.024 | 0.126 |
| CIDI-SF ~ | C2 | -0.007 | 0.022 | 0.752 |
| CIDI-SF ~ | C3 | -0.027 | 0.022 | 0.230 |
| CIDI-SF ~ | C4 | 0.012 | 0.022 | 0.569 |
| Neuroticism+Resilience ~ | PRS | 0.040 | 0.005 | < 0.001 |
| Neuroticism+Resilience ~ | Sex | 0.090 | 0.010 | < 0.001 |
| Neuroticism+Resilience ~ | Age _{t1} | -0.067 | 0.025 | 0.009 |
| Neuroticism+Resilience ~ | Age _{t2} | 0.034 | 0.025 | 0.167 |
| Neuroticism+Resilience ~ | C1 | 0.005 | 0.003 | 0.116 |
| Neuroticism+Resilience ~ | C2 | 0.005 | 0.003 | 0.071 |
| Neuroticism+Resilience ~ | C3 | -0.012 | 0.003 | < 0.001 |
| Neuroticism+Resilience ~ | C4 | 0.008 | 0.003 | 0.010 |

Abbreviations: Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale