**Supplements**

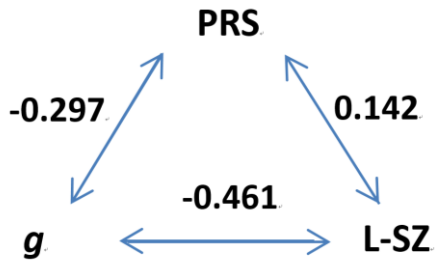


**Figure 1. Phenotypic correlations: *L-SZ* and *PRS* (biserial), *L-SZ* and *g* (biserial), *g* and *PRS* (Pearson)**

*L-SZ* = schizophrenia liability; *PRS* = polygenic risk score; *g* = general cognitive ability. *L-SZ* correlated with *g* at -0.461 and *PRS* at 0.142 (both *p*-value < 0.001). The Pearson correlation between *g* and *PRS* is -0.297 (*p*-value < 0.001).

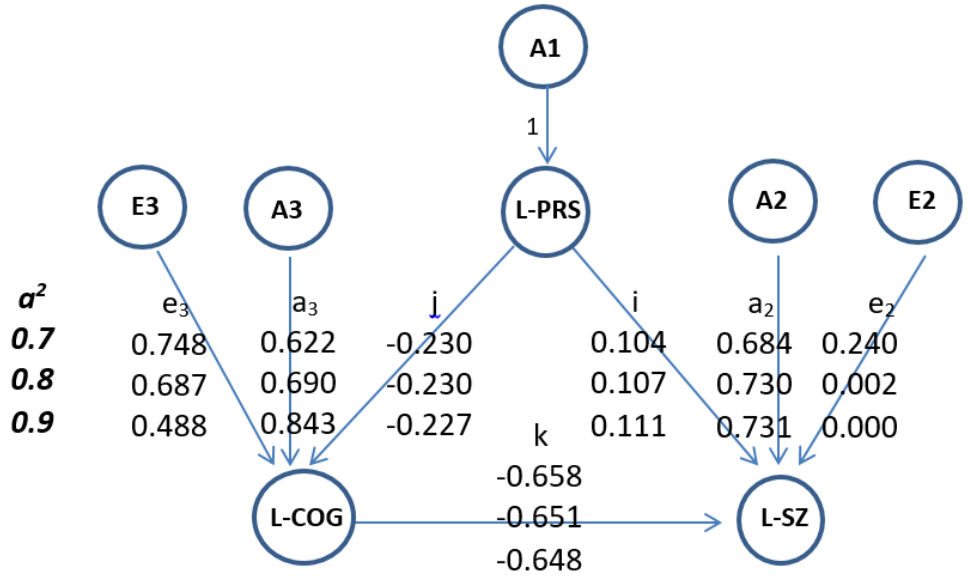


**Figure 2. Standardized parameter estimation of model 4 with $a^2$ of schizophrenia at 0.7~0.9**

The parameter estimations with heritability $a^2$ of schizophrenia at 0.7, 0.8 and 0.9 are listed in the 1st, 2nd and 3rd rows respectively. *L-PRS* = polygenic risk score; latent variables: *L-SZ* = schizophrenia liability; *L-COG* = general cognitive factor; *A*=genetic component; *E*= environmental component; *i*, *j*, *k* represent causal paths; causal path *i*, *L-PRS* to *L-SZ*; causal path *j*, *L-PRS* to *L-COG*; causal path *k*, *L-COG* to *L-SZ*; $a^2$ = overall genetic variance to *L-SZ* is constrained to 0.7, 0.8, 0.9. When schizophrenia heritability $a^2$ increases, genetic parameters ($a_2$ and $a_3$) increase and environmental parameters ($e_2$ and $e_3$) decrease.

**Table 1. Statistics for *PRS* in schizophrenia, siblings and control groups**

| Polygenic Risk Score (*PRS*) | *p*-value cut-off | Control | | Siblings | | SZ | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD |
| N. | | 607 | | 286 | | 416 | |
| Level 1 | 5.00E-08 | -0.517 | 0.264 | -0.486 | 0.257 | -0.444 | 0.268 |
| Level 2 | 1.00E-06 | -0.977 | 0.368 | -0.905 | 0.366 | -0.835 | 0.367 |
| Level 3 | 1.00E-04 | -1.404 | 0.735 | -1.239 | 0.722 | -0.956 | 0.690 |
| Level 4 | 1.00E-03 | -1.465 | 1.080 | -1.241 | 1.000 | -0.745 | 1.059 |
| Level 5 | 1.00E-02 | -8.611 | 1.690 | -8.053 | 1.614 | -7.368 | 1.660 |
| Level 6 | 5.00E-02 | -12.333 | 2.382 | -11.562 | 2.259 | -10.480 | 2.492 |
| Level 7 | 1.00E-01 | -13.246 | 2.670 | -12.402 | 2.605 | -11.185 | 2.843 |
| Level 8 | 2.00E-01 | -14.475 | 3.001 | -13.608 | 2.943 | -12.242 | 3.185 |
| Level 9 | 5.00E-01 | -18.995 | 3.268 | -18.049 | 3.176 | -16.604 | 3.455 |
| Level 10 | 1.00E+00 | -19.707 | 3.282 | -18.772 | 3.204 | -17.347 | 3.481 |

Ten different *PRS* levels were calculated based on the SNPs associated with schizophrenia at different *p*-value thresholds ($P_T < 5\times10^{-08}$, $1\times10^{-06}$, $1\times10^{-04}$, $1\times10^{-03}$, 0.01, 0.05, 0.1, 0.2, 0.5, 1). *SD* = standard deviation; *SZ* = schizophrenia group.

**Table 2. Logistic Regression results for every *p*-value level**

| Level | *p*-value cut-off | Approx #SNPs | Cox & Snell R Square | *P* value for coefficients |
|---|---|---|---|---|
| **1** | 5.00E-08 | 106 | 0.001 | 1.01E-04 |
| **2** | 1.00E-06 | 238 | 0* | 6.93E-08 |
| **3** | 1.00E-04 | 1,252 | 0.001 | 5.38E-18 |
| **4** | 1.00E-03 | 3,368 | 0* | 6.18E-21 |
| **5** | 1.00E-02 | 10,572 | 0.027 | 6.48E-23 |
| **6** | **5.00E-02** | **24,694** | **0.09** | **1.16E-24** |
| **7** | 1.00E-01 | 35,816 | 0.088 | 4.46E-24 |
| **8** | 2.00E-01 | 51,895 | 0.083 | 4.33E-23 |
| **9** | 5.00E-01 | 81,383 | 0.081 | 1.90E-22 |
| **10** | 1.00E+00 | 102,488 | 0.078 | 9.17E-22 |

*0: the value is less than the 0.001; Approx #SNPs: N. of the SNPs

**Table 3. Sensitivity analyses for bi-variate and tri-variate models**

| $a^2$ | Model | *ep* | -2LL | *df* | AIC | Δ-2LL | Δ*df* | *p* | comp. |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Bi-variate model** | | | | | | |
| 0.7 | 1: Cholesky | 29 | 26061 | 8446 | 9168.8 | | | | |
| | 2: L-COG<->L-SZ | 29 | 26061 | 8446 | 9168.8 | | | | |
| | 3: dropping L-SZ→ L-COG | 28 | 26062 | 8447 | 9167.81 | 1.01 | 1 | 0.32 | 1&2 |
| | 4: dropping L-COG→ L-SZ | 28 | 26073 | 8447 | 9178.77 | 11.97 | 1 | <0.01 | 1&2 |
| 0.8 | 1: Cholesky | 29 | 26070 | 8446 | 9177.51 | | | | |
| | 2: L-COG<->L-SZ | 29 | 26070 | 8446 | 9177.51 | | | | |
| | 3: dropping L-SZ→ L-COG | 28 | 26070 | 8447 | 9176.2 | 0.69 | 1 | 0.41 | 1&2 |
| | 4: dropping L-COG→L-SZ | 28 | 26088 | 8447 | 9194.12 | 18.61 | 1 | <0.01 | 1&2 |
| 0.9 | 1: Cholesky | 29 | 26084 | 8446 | 9191.93 | | | | |
| | 2: L-COG<->L-SZ | 29 | 26084 | 8446 | 9191.93 | | | | |
| | 3: dropping L-SZ→ L-COG | 28 | 26095 | 8447 | 9201.12 | 11.19 | 1 | <0.01 | 1&2 |
| | 4: dropping L-COG→L-SZ | 28 | 26107 | 8447 | 9213.28 | 23.33 | 1 | <0.01 | 1&2 |
| | | | **Tri-variate model** | | | | | | |
| 0.7 | 1: Full | 32 | 29726.49 | 9752 | 10222.49 | | | | |
| | 2: dropping PRS→ L-COG (j) | 31 | 29730.97 | 9753 | 10224.97 | 4.48 | 1 | 0.03 | 1 |
| | 3: dropping PRS → L-SZ (i) | 31 | 29730.75 | 9753 | 10224.75 | 4.27 | 1 | 0.04 | 1 |
| | 4: dropping L-SZ → L-COG (k') | 31 | 29727.35 | 9753 | 10221.35 | 0.86 | 1 | 0.35 | 1 |
| | 5: dropping L-COG → L-SZ (k) | 31 | 29739.25 | 9753 | 10233.25 | 12.76 | 1 | <0.01 | 1 |
| 0.8 | 1: Full | 32 | 29734.4 | 9752 | 10230.4 | | | | |
| | 2: dropping PRS→ L-COG (j) | 31 | 29756.77 | 9753 | 10250.77 | 22.37 | 1 | <0.01 | 1 |
| | 3: dropping PRS → L-SZ (i) | 31 | 29746.82 | 9753 | 10240.82 | 12.42 | 1 | <0.01 | 1 |
| | 4: dropping L-SZ → L-COG (k') | 31 | 29734.72 | 9753 | 10228.72 | 0.32 | 1 | 0.57 | 1 |
| | 5: dropping L-COG → L-SZ (k) | 31 | 29754.58 | 9753 | 10248.58 | 20.19 | 1 | <0.01 | 1 |
| 0.9 | 1: Full | 32 | 29748.67 | 9752 | 10244.67 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2: dropping PRS→ L-COG (j) | 31 | 29770.35 | 9753 | 10264.35 | 21.68 | 1 | <0.01 | 1 |
| 3: dropping PRS → L-SZ (i) | 31 | 29774.54 | 9753 | 10268.54 | 25.87 | 1 | <0.01 | 1 |
| 4: dropping L-SZ → L-COG (k') | 31 | 29759.66 | 9753 | 10253.66 | 10.99 | 1 | <0.01 | 1 |
| 5: dropping L-COG → L-SZ (k) | 31 | 29773.71 | 9753 | 10267.71 | 25.04 | 1 | <0.01 | 1 |

$a^2$ = overall genetic variance to *L-SZ* is constrained to 0.7, 0.8, 0.9; *ep*=estimate parameter; −2LL=minus 2 log likelihood; *df*=degree of freedom; AIC=Akaike information criterion; Δ-2LL=the difference of minus 2 log likelihood between two models; Δ*df*=the difference of the degree of freedom; *p* = *p*-value, when *p* value < 0.05 (*p*-value <0.025 for bi-variate), the model is significantly worse than its comparison model; comp. = the comparison model; latent variables: *L-SZ* = schizophrenia liability, *L-COG* = general cognitive factor. *Bi-variate models*: when $a^2$ is 0.7 to 0.8, model 4 deteriorates statistically significantly from baseline models, while model 3 is not significantly worse and thus the model with the best fit for the data. When $a^2$ is 0.9, both models 3 and 4 are significantly worse than the baseline model (model 2), and model 3 is still chosen due to the smaller AIC. So, the model fitting results do not change with different heritability levels. *Tri-variate models*: When the heritability of schizophrenia is set to 0.7 and 0.8, the model fitting results are similar and model selections are the same as the results when the heritability of schizophrenia 0.82. When it is fixed to 0.9, all nested models (model 2~5) are significantly worse than model 1, and could not select the model according to *p*-value; however model 4 still has the smallest AIC among them, and fits the data best.

**Table 4. The path from A and E of the first phenotype to the second phenotype**

| $a^2$ | *L-SZ→L-COG* | | | | *L-COG →L-SZ* | | | |
|---|---|---|---|---|---|---|---|---|
| | **A** | | **E** | | **A** | | **E** | |
| | Cholesky $a_{21}$' | causal $a_1$'*k' | Cholesky $e_{21}$' | causal $e_1$'*k' | Cholesky $a_{21}$ | causal $a_1$*k | Cholesky $e_{21}$ | causal $e_1$*k |
| **0.82** | -0.421 | -0.628 | -0.712 | -0.294 | -0.545 | -0.531 | -0.424 | -0.424 |
| | -0.501~ -0.339 | -0.661~ -0.594 | -0.850~ -0.566 | -0.310~ -0.278 | -0.642~ -0.487 | -0.572~ -0.486 | -0.425~ -0.355 | -0.427~ -0.395 |
| **0.70** | -0.365 | -0.580 | -0.689 | -0.380 | -0.422 | -0.466 | -0.548 | -0.504 |
| | -0.483~ -0.265 | -0.610~ -0.549 | -0.820~-0.524 | -0.399~-0.359 | -0.557~ -0.357 | -0.519~ -.401 | -0.577~ -0.422 | -0.521~ -0.458 |
| **0.80** | -0.408 | -0.621 | -0.711 | -0.310 | -0.519 | -0.512 | -0.447 | -0.447 |
| | -0.494~ -0.324 | -0.653~ -0.587 | -0.846~-0.561 | -0.326~ -0.293 | -0.615~ -0.464 | -0.554~ -0.316 | -0.457~ -0.370 | -0.502~ -0.398 |
| **0.90** | -0.480 | -0.660 | -0.720 | -0.220 | -0.658 | -0.600 | -0.316 | -0.320 |
| | -0.545~ -0.414 | -0.691~ -0.621 | -0.856~ -0.573 | -0.230~ -0.207 | -0.797~ -0.588 | -0.641~ -0.563 | -0.376~ -0.284 | -0.343~ -0.296 |

Parameter comparison like the value of $a_{21}$ and $a_1*k$ (figure 1 main paper) at different schizophrenia heritability $a^2$ levels with confidence intervals (CIs); Latent variables: *L-SZ* = schizophrenia liability, *L-COG* = general cognitive factor; *A* = genetic component; *E*= environmental component; Cholesky = Cholesky model; causal = causal model, $a^2$ = overall genetic variance to *L-SZ* is constrained to 0.7, 0.8, 0.9 and 0.82; CIs that do not include 0 are significant. The value of *A* and *E* contribution on the second phenotype is closer between the Cholesky model and nested causal model in *L-COG* → *L-SZ* at all heritability levels. The findings duplicate and verify the results of the model fitting comparison, which supports a direction of causation from cognition to schizophrenia liability (see main paper).

**Table 5. Genetic variance components of schizophrenia liability contributed by *L-PRS***

| $a^2$ | *L-PRS* directly | | *L-PRS* through *L-COG* | | Covariance between *L-PRS* & *L-COG* | | Total variance through *L-PRS* |
|---|---|---|---|---|---|---|---|
| | $i^2 \times {a_1}^2$ | | $(k \times j)^2 \times {a_1}^2$ | | $2 \times k \times j \times i \times {a_1}^2$ | | |
| 0.7 | 0.0108 | 1.55% | 0.0228 | 3.26% | 0.0314 | 4.49% | 9.30% |
| | 0.0053~0.0224 | 0.76~3.20% | 0.0154~0.0357 | 2.19~5.10% | 0.0155~0.0413 | 2.21~5.89% | 6.25~12.22% |
| 0.8 | 0.0115 | 1.44% | 0.0224 | 2.79% | 0.0321 | 4.01% | 8.24% |
| | 0.0044~0.0152 | 0.55~1.90% | 0.0165~0.0280 | 2.06~3.50% | 0.0226~0.0374 | 2.82~4.67% | 6.53~10.26% |
| 0.9 | 0.0123 | 1.37% | 0.0217 | 2.41% | 0.0327 | 3.64% | 7.42% |
| | 0.0081~0.0176 | 0.90~1.96% | 0.0184~0.0290 | 2.04~3.22% | 0.0271~0.0416 | 3.01~4.62% | 6.10~10.31% |

Overall genetic variance components of schizophrenia liability related to *L-SZ* when $a^2$ is constrained to 0.7, 0.8, and 0.9. $a^2$ = overall genetic variance; %: percentage of genetic variance components of schizophrenia liability with confidence intervals (*CIs*); latent variables: *L-SZ* = schizophrenia liability; *L-COG* = general cognitive factor; *L-PRS*= polygenic risk score; *i*, *j*, *k* represent causal paths: causal path *i*, *L-PRS* to *L-SZ*; causal path *j*, *L-PRS* to *L-COG*; causal path *k*, *L-COG* to *L-SZ* (figure 2 in main paper); $a_m$ is the path coefficient from the $m^{th}$ genetic factor to the latent variable in figure 2 in main paper; CIs that do not include 0 are significant. The amount of every component of genetic variance of schizophrenia liability accounted by *L-PRS* is similar at different $a^2$ levels, with percentages decreasing as $a^2$ increases: 9.3% of the schizophrenia genetic variance is explained by *L-PRS* at $a^2$=0.7 and 7.4% at $a^2$=0.9.

**Table 6. Genetic variance components of schizophrenia liability related *L-COG***

| $a^2$ | From *L-COG* excluded *L-PRS* | | *L-PRS* through *L-COG* | | Covariance between *L-PRS* & *L-COG* | | Total variance Related *L-COG* |
|---|---|---|---|---|---|---|---|
| | $k^2 \times {a_3}^2$ | | $(k \times j)^2 \times {a_1}^2$ | | $2 \times k \times j \times i \times {a_1}^2$ | | |
| 0.7 | 0.1675 | 23.93% | 0.0228 | 3.26% | 0.0314 | 4.49% | 31.68% |
| | 0.0979~0.2391 | 13.98~34.16% | 0.0154~0.0357 | 2.19~5.10% | 0.0155~0.0413 | 2.21~5.89% | 23.20~42.60% |
| 0.8 | 0.2019 | 25.23% | 0.0224 | 2.79% | 0.0321 | 4.01% | 32.04% |
| | 0.1789~0.2548 | 22.37~31.85% | 0.0165~0.0280 | 2.06~3.50% | 0.0226~0.0374 | 2.82~4.67% | 26.17~37.12% |
| 0.9 | 0.2986 | 33.18% | 0.0217 | 2.41% | 0.0327 | 3.64% | 39.23% |
| | 0.2714~0.3503 | 30.16~38.92% | 0.0184~0.0290 | 2.04~3.22% | 0.0271~0.0416 | 3.01~4.62% | 33.16~44.48% |

Overall genetic variance components of schizophrenia liability related to *L-COG* when $a^2$ is constrained to 0.7, 0.8, and 0.9. $a^2$ = overall genetic variance; %: percentage of genetic variance components of schizophrenia liability with confidence intervals (*CIs*); latent variables: *L-SZ* = schizophrenia liability; *L-COG* = general cognitive factor; *L-PRS*= polygenic risk score; *i*, *j*, *k* represent causal paths: causal path *i*, *L-PRS* to *L-SZ*; causal path *j*, *L-PRS* to *L-COG*; causal path *k*, *L-COG* to *L-SZ* (figure 2 in main paper); $a_m$ is the path coefficient from the $m^{th}$ genetic factor to the latent variable in figure 2 in main paper; CIs that do not include 0 are significant. The total variance related to *L-COG* increases as $a^2$ increases from 0.7 to 0.9.