Heritable Variation, With Little or No Maternal Genetics Contribution, Accounts for Recurrence Risk to Autism Spectrum Disorder in Sweden

Supplemental Information

Table S1. Estimated variance components for liability before they are transformed to fractions of variation explained. Separate outcomes fit for Autism Spectrum Disorder (ASD), Autistic Disorder (AD) and Spectrum Disorder (SD).

Estimates[a] (95% CI[b])	Outcome		
	ASD	AD	SD
Estimated variance for random components[c]			
Maternal effect	0.024 (0, 0.275)	0.006 (0, 0.292)	0.031 (0, 0.247)
Additive genetic effect	5.750 (3.983, 6.860)	4.083 (2.654, 5.716)	3.360 (2.411, 4.704)
Shared environmental effect	0.010 (0, 0.191)	0.038 (0, 0.393)	0.009 (0, 0.169)
Estimated coefficient for fixed parameters[d]			
Sex: male	0.394 (0.385, 0.401)	0.374 (0.362, 0.387)	0.356 (0.350, 0.367)
Birth cohort: 2003-07	-0.246 (-0.259, -0.237)	-0.092 (-0.104, -0.077)	-0.324 (-0.338, -0.309)

[a] The mixed model used the probit link. Random effects in the liability model included maternal, additive genetic, shared environmental and unshared environmental effects, together with sex (1=male, 0=female) and birth cohort (1=2003-2007 cohort, 0=1998-2002 cohort) as fixed parameters. Coefficients for fixed effects indicate risk for outcome associated with the variable, after adjustment for other parameters.

[b] CI: Confidence interval.

[c] Unshared environmental effect not shown because it is the residual variance and set to 1 in our model.

[d] The reported probit-link values for fixed parameters are in standard normal quantile scale, which could be transformed to values comparable to Generalized Linear Mixed Model (GLMM) without random components by multiplying by $\sqrt{(\sigma_A^2 + \sigma_M^2 + \sigma_C^2 + 1)}$, where A denotes additive genetic effect, M denotes maternal effect, and C denotes shared environmental effect.

Table S2. Estimated variance components for liability fitting maternal and paternal additive genetic effects separately, as a check for robustness of the results from the primary model. Separate outcomes fit for Autism Spectrum Disorder (ASD), Autistic Disorder (AD) and Spectrum Disorder (SD).

Estimates[a] (95% CI[b])	Outcome		
	ASD	AD	SD
Estimated variance for random components (fractions of variation explained)			
Maternal effect	0.002 (0, 0.043)	0.004 (0, 0.088)	0.005 (0, 0.075)
Additive genetic effect: maternal contributes	0.478 (0.294, 0.653)	0.407 (0.173, 0.641)	0.368 (0.175, 0.582)
Additive genetic effect: paternal contributes	0.378 (0.199, 0.549)	0.391 (0.164, 0.627)	0.403 (0.201, 0.616)
Shared environmental effect	0.001 (0, 0.033)	0.006 (0, 0.088)	0.002 (0, 0.054)
Unshared environmental effect	0.141 (0.100, 0.212)	0.192 (0.115, 0.325)	0.222 (0.133, 0.326)
Estimated coefficient for fixed parameters[c]			
Sex: male	0.397 (0.389, 0.405)	0.373 (0.361, 0.386)	0.361 (0.351, 0.371)
Birth cohort: 2003-07	-0.245 (-0.255, -0.235)	-0.091 (-0.105, -0.077)	-0.322 (-0.338, -0.307)

[a] The mixed model used the probit link. Random effects in the liability model included maternal, additive genetic, shared environmental and unshared environmental effects, together with sex (1=male, 0=female) and birth cohort (1=2003-2007 cohort, 0=1998-2002 cohort) as fixed parameters. Coefficients for fixed effects indicate risk for outcome associated with the variable, after adjustment for other parameters.

[b] CI: Confidence interval.

[c] The reported probit-link values for fixed parameters are in standard normal quantile scale, which could be transformed to values comparable to Generalized Linear Mixed Model (GLMM) without random components by multiplying by $\sqrt{\left(\sigma_{Am}^2 + \sigma_{Ap}^2 + \sigma_M^2 + \sigma_C^2 + 1\right)}$, where Am denotes additive genetic effect-maternal contributes, Am denotes additive genetic effect-paternal contributes, M denotes maternal effect, and C denotes shared environmental effect.

Table S3. Estimated fraction of variation explained for the liability of ASD, AD and SD, and estimated coefficient for fixed parameters, half siblings excluded. Separate outcomes fit for Autism Spectrum Disorder (ASD), Autistic Disorder (AD) and Spectrum Disorder (SD).

Estimates[a] (95% CI[b])	Outcome		
	ASD	AD	SD
Estimated variance for random components (fractions of variation explained)			
Maternal effect	0.008 (0, 0.052)	0.005 (0, 0.083)	0.043 (0, 0.116)
Additive genetic effect	0.837 (0.721, 0.873)	0.790 (0.609, 0.848)	0.689 (0.551, 0.816)
Shared environmental effect	0.000 (0, 0.031)	0.006 (0, 0.086)	0.004 (0, 0.055)
Unshared environmental effect	0.155 (0.121, 0.217)	0.198 (0.138, 0.278)	0.264 (0.167, 0.345)
Estimated coefficient for fixed parameters[c]			
Sex: male	0.399 (0.391, 0.407)	0.371 (0.353, 0.376)	0.363 (0.351, 0.371)
Birth cohort: 2003-07	-0.242 (-0.253, -0.231)	-0.090 (-0.113, -0.083)	-0.317 (-0.334, -0.303)

[a] The mixed model used the probit link. Random effects in the liability model included maternal, additive genetic, shared environmental and unshared environmental effects, together with sex (1=male, 0=female) and birth cohort (1=2003-2007 cohort, 0=1998-2002 cohort) as fixed parameters. Coefficients for fixed effects indicate risk for outcome associated with the variable, after adjustment for other parameters.

[b] CI: Confidence interval.

[c] The reported probit-link values for fixed parameters are in standard normal quantile scale, which could be transformed to values comparable to Generalized Linear Mixed Model (GLMM) without random components by multiplying by $\sqrt{(\sigma_A^2 + \sigma_M^2 + \sigma_C^2 + 1)}$, where A denotes additive genetic effect, M denotes maternal effect, and C denotes shared environmental effect.

Supplemental Note

Diagnosis

At age 4 years, a mandatory developmental assessment, consisting of motor, language, cognitive, and social development, is conducted on all Swedish children. Children with a suspected developmental disorder are referred for further assessment by a specialized team who report diagnostic information to the National Patient Register. The International Classification of Diseases (ICD) 10th revision, introduced in Sweden in 1997, is used for all diagnoses in the register from 1997 and onwards. We have included cases with a diagnosis of autistic disorder (AD; ICD-10 code F84.0); for SD, we include Asperger's syndrome (AS; ICD-10 code F84.5) and/or pervasive developmental disorder not otherwise specified (PDD-NOS; ICD-10 code F84.9). A child is considered affected if she or he is given an AD or SD diagnosis prior to 31st December 2014. If multiple codes for our outcome measure are specified for a child, the code selected on the basis of the algorithm: if ever Rett's (ICD-10 code F84.2) or CDD, then assign Rett or CDD; if never Rett's or CDD, then AD (Autistic disorder/childhood autism) is subtype if ever received this diagnosis (disregard other ASD subtype diagnoses). If never AD and ever had Asperger disorder, then assign Asperger's Syndrome (AS) diagnosis (disregard other ASD subtypes). If never AD, and never AS, and ever (PDD-NOS or ATYPICAL or other PDD) then assign PDD-NOS.

Description of Complementary Analyses

Here we take a complementary approach to computing risk and family recurrence risk (FRR) to that presented in the body of the manuscript. In the manuscript we use a structured or hierarchical classification of subjects into pairs, starting with cousins, whereas here we use

an unstructured approach to counting relative pairs. We therefore call the recurrence risk computed here the unstructured recurrence risk (uRR) and the unstructured family recurrence risk (uFRR).

We begin data analysis with 14,553 ASD cases, separated by severity into 6,355 AD and 8,198 SD, and 947,079 unaffected controls. In our cohort of children born 1998 to 2007, prevalences for ASD, AD, and SD are 0.0151, 0.0066, and 0.0085, respectively. After removing individuals with only one known parent, a total of 14,408, 6,283, 8,125, and 937,647 ASD, AD, SD and unaffected controls, remained. Note the loss of case individuals is relatively equivalent across diagnostic types: 1.0%, 1.1%, and 0.9%. This is also similar to the loss in the controls of 1.0%.

Per the body of the manuscript, there are 7 relationship types: full sibs (FS), paternal and maternal half sibs (pHS, mHS), and 4 different cousin types depending on whether the two parents responsible for the cousin relationship are sisters (maternal parallel cousins, mPC), brothers (paternal parallel cousins, pPC), or a sister and brother. These last pairs are cross cousins (CC). Here, unlike the body of the manuscript, we retain CC lineages: we call the pair pCC if the index cousin is related through his/her father and mCC otherwise. Individuals can contribute to multiple relationship types. For first and second degree relatives, only knowledge of parents is required; for cousins, knowledge of grandparents of maternal or paternal lineage, as appropriate for pedigree relationships, is required. Next we sought to determine whether the family structure in families of ASD subjects is similar to the family structure of the control subjects (Tables S4-S6). Information for an index case would be excluded from the analyses if the required pedigree information were absent or if the subject did not have relatives of the required type.

Table S4. Number of cases and controls with required pedigree information and relatives for **ASD** probands

	Have Required Pedigree Information		Have Relatives of Specified Type	
Relationship	Cases	Controls[a]	Cases	Controls
FS	14,408	14,408	7,709	8,440
mHS	14,408	14,408	946	515
pHS	14,408	14,408	807	474
mPC	12,478	12,331	2,943	3,216
mCC	12,478	12,330	2,774	3,039
pCC	12,311	12,245	2,772	3,024
pPC	12,311	12,239	2,746	3,084

[a] For controls, we took the mean of 100 replicated samples.

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Table S5. Number of cases and controls with required pedigree information and relatives for **AD** probands

	Have Required Pedigree Information		Have Relatives of Specified Type	
Relationship	Cases	Controls[a]	Cases	Controls
FS	6,283	6,283	3,262	3,660
mHS	6,283	6,283	345	225
pHS	6,283	6,283	298	205
mPC	5,067	5,379	1,206	1,393
mCC	5,067	5,379	1,148	1,316
pCC	5,022	5,339	1,121	1,319
pPC	5,022	5,340	1,108	1,338

[a] For controls, we took the mean of 100 replicated samples.

Notes: FS full sibs, mHS maternal half sibs, pHS paternal parallel cousins, mPC maternal parallel cousins, mCC maternal cross cousins, pCC paternal cross cousins, pPC paternal parallel cousins.

Table S6. Number of cases and controls with required pedigree information and relatives for **SD** probands.

	Have Required Pedigree Information		Have Relatives of Specified Type	
Relationship	Cases	Controls[a]	Cases	Controls
FS	8,125	8,125	4,206	4,739
mHS	8,125	8,125	572	294
pHS	8,125	8,125	479	267
mPC	7,411	6,955	1,714	1,812
mCC	7,411	6,960	1,606	1,711
pCC	7,289	6,900	1,636	1,702
pPC	7,289	6,901	1,622	1,735

[a] For controls, we took the mean of 100 replicated samples.

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Whether the index subjects are cases or controls, the number of pedigrees with complete information tends to be the same for all types of relatives (Table S4). Except for relatives of half-siblings, families with at least one ASD index case are less likely to have additional family members for all relative types (Table S4). Curiously, families with at least one ASD case are more likely to have half sib relatives. Thus there could be a relationship between the genetic load for ASD and the chance of having children with more than one partner. This "half-sibling" pattern is seen also for the two sub-diagnoses (Tables S5-S6). Another curious pattern in the data is the difference between AD and SD index subjects for information on third degree relatives; there is a small bias toward complete information on grandparents for families accessed through index subjects who are unaffected (controls) relative to AD index subjects and vice versa for SD subjects. It seems possible there is a relationship between the genetic load for AD and the completeness of pedigree information, although its effect on calculations of uFRR should be small.

We next sought to quantify the risk of having relatives with ASD, AD, and SD when the index individuals were unaffected; recall that the sample size for control index individuals was set by the number of subjects of a diagnostic type in the sample. Here we report mean values from 100 random samples (Table S7) and note the expected value should typically reflect the population prevalence of the disorder. For full siblings and cousins the risk of having a relative with ASD or subtype is similar to the population prevalence; however, the risks for half sibs varies between 1.5 and 2 times the population prevalence. Again the data point to a possible relationship between risk of having a child with ASD and having children with more than one partner. To test whether the mHS and pHS risk is significantly different from the population value, we assume the overall prevalence of 0.0156 to be the true value and treat the observed rate in 100 replicate samples as the data; then the test is a one-sample t-text with 99 degrees of freedom, and both risks are significantly different from the population prevalence (pHS, 3.6×10^{-7}; mHS, 1.9×10^{-5}).

Table S7. Proportion of ASD, AD, and SD in relatives of controls.

	Diagnosis		
Relationship	ASD	AD	SD
FS	0.0126	0.0057	0.0073
mHS	0.0283	0.0097	0.0178
pHS	0.0234	0.0096	0.0169
mPC	0.0140	0.0058	0.0083
mCC	0.0141	0.0059	0.0081
pCC	0.0138	0.0060	0.0084
pPC	0.0137	0.0058	0.0081

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Consistent with a strongly genetic disorder, and results for the Liability Model, the risk of having a relative with ASD when the index subjects are themselves affected is notably larger for each of the three diagnostic groups and all relative types (Table S8) than that seen for controls (Table S7). Notably, severity of ASD for the index case tends to be tied to a greater risk for ASD in relatives, although less so for lower risks in cousins (Table S8). There is a gradual decrease in risk from full sibs to half sibs to cousins, consistent with an additive genetic effect. The difference in risk between mPC and the other cousin types shows some evidence of a possible maternal genetic effect because mPC cousins share a maternal genetic component that does not influence the other three cousin types. Similarly, the difference in risk between the mHS and pHS indicates a possible total maternal effect (genetic and environmental). This is a component shared by mHS but not by pHS.

Table S8. Risk of ASD in relatives of ASD, AD, and SD cases.

	Diagnosis		
Relationship	ASD	AD	SD
FS	0.1060	0.1152	0.0989
mHS	0.0659	0.0792	0.0577
pHS	0.0656	0.0760	0.0589
mPC	0.0333	0.0305	0.0353
mCC	0.0290	0.0293	0.0287
pCC	0.0284	0.0300	0.0273
pPC	0.0295	0.0280	0.0305

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

To determine risks and uFRR, we define an index group as either all cases or a sample of controls of the same size as the number of cases. For each of the index individuals we then determined the fraction of relatives of a certain type with a case diagnosis (ASD, AD, or SD). The unstructured recurrence risk is then the sum of these fractions divided by the number of individuals in the index group with at least 1 relative of the required type. Mathematically, for t = 1, …, T sibships, the unstructured recurrence risk K is calculated as:

$$K = \frac{\sum_{t=1}^{T} a_t(a_t-1)}{\sum_{t=1}^{T} a_t(s_t-1)} \qquad a_t = \#\text{affected sibs in sibship t}, \quad s_t = \#\text{sibs in sibship t}$$

Table S9. Unstructured family recurrence risks (uFRRs) for ASD when family accessed through ASD, AD, and SD index.

	Diagnosis		
Relationship	ASD	AD	SD
FS	8.40	9.14	7.85
mHS	2.33	2.80	2.04
pHS	2.81	3.25	2.52
mPC	2.38	2.18	2.52
mCC	2.06	2.08	2.04
pCC	2.07	2.17	1.98
pPC	2.15	2.04	2.23

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

For the uFRR, we first allow the diagnosis of the affected relative to be ASD, ignoring severity, while the index subjects were either ASD or one of the severity subtypes. The uFRR is calculated using the risks in Table S8 divided by the rate of ASD computed when the index subjects were controls (Table S7, column ASD). As noted previously, there is a steady decline in uFRR from first to third degree relatives (Table S9). Nonetheless, consistent with the perturbation observed in risk for half-siblings, specifically the elevated unstructured

recurrence risk when the index is unaffected and she or he has a half-sibling, the uFRR for half-siblings is smaller than one would expect for a simple additive model. uFRR for sister-sister cousins also tend to have greater uFRR than other cousin pairings, regardless of diagnosis, consistent with the possibility of a modest maternal genetic effect.

Next, we forced the relative to have the same diagnosis as the index cases. Here the uFRR changes for the severity subtypes due to the change in denominator, the recurrence risk for the subtype from index subjects who are controls (Table S7), as well as by forcing index subjects and relatives to match on diagnosis (Table S10).

Table S10. Unstructured Recurrence risk (proportions) and unstructured family recurrence risks (uFRRs) for ASD, AD, and SD.

Relationship	Diagnosis					
	ASD		AD		SD	
	risk	uFRR	risk	uFRR	risk	uFRR
FS	0.1060	8.40	0.0766	13.55	0.0683	9.42
mHS	0.0659	2.33	0.0338	3.49	0.0294	1.66
pHS	0.0656	2.81	0.0233	2.43	0.0303	1.79
mPC	0.0333	2.38	0.0115	1.96	0.0236	2.83
mCC	0.0290	2.06	0.0116	1.98	0.0158	1.95
pCC	0.0284	2.07	0.0143	2.38	0.0168	2.01
pPC	0.0295	2.15	0.0134	2.31	0.0228	2.81

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Here the uFRR show more variability, and in part that is undoubtedly due to greater sampling error. Nonetheless the uFRR for AD tends to be greater than that for SD for full siblings and half-siblings. Also, for half-siblings, the higher uFRR for maternal versus paternal origin is consistent with a maternal effect that is environmental, because the cousins show pattern inconsistent with a maternal genetic effect. By contrast, for SD there is

no difference for FRR for half-siblings, whereas there is some evidence for a maternal genetic effect from cousins.

In the next steps, we use a method of moments approach to translate the unstructured recurrence risk into additive genetic, maternal and shared environmental effects, based on the results thus far and assumed contribution of each of these effects for each of the relative types (Table S11).

Table S11. Contributions of the different components to risk.

Relationship	Additive Genetic	Maternal	Shared Environment
FS	0.50	1	1
mHS	0.25	1	1
pHS	0.25	0	0
mPC	0.125	0.50	0
mCC	0.125	0	0
pCC	0.125	0	0
pPC	0.125	0	0

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Lynch and Walsh (1998, Chapter 25:730-736) summarizes three different approaches to determine the regression coefficient on the underlying scale (0-1 being the observed scale) from the comparison of recurrence risk in cases to the risk in controls. Results, not shown here, for these three approaches show a correlation r > 0.999 for these data and therefore the results from Lynch and Walsh, formula 25.1a, was used:

$$b = \frac{(x_{control} - x_{case})\Phi_{control}}{p(x_{control})},$$

where $\Phi_{control}$ is the risk in controls, x_i is such that $P(X > x_i) = \Phi_i$ and $p(x_{control})$ is the height of the normal distribution at $x_{control}$. Applying this formula to the data results in estimates of b (Table S12).

Table S12. Estimates of the regression coefficient b on the underlying scale for the three diagnosis.

	Diagnosis		
Relationship	ASD	AD	SD
FS	0.383	0.387	0.344
mHS	0.174	0.191	0.086
pHS	0.203	0.131	0.099
mPC	0.142	0.088	0.151
mCC	0.117	0.087	0.093
pCC	0.117	0.114	0.098
pPC	0.124	0.109	0.148

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Least squares estimates for the three variance components (Table S13) can be obtained by equating the estimated regression coefficients from Table S12 to the expectations from Table S11. The great bulk of the variability in diagnosis is consistent with additive genetic effects, consistent with modeling reported in the body of the manuscript. Likewise, our results suggest that maternal effects play a minor role in the risk of ASD, if any, as estimates would not be significantly different from zero.

Table S13. Least squares estimates for fraction of variation explained by the different components on the underlying scale for the three diagnoses. Estimates less than 0 were set to 0.

	Diagnosis		
Component	ASD	AD	SD
Additive	0.86	0.68	0.70
Maternal	0.07	0.01	0.12
Shared environment	0.00	0.03	0.00

Finally, we ask this question: if a family is ascertained through a proband diagnosed with severity subtype AD (or SD), how does that influence the diagnostic subtype of other family

members? For AD probands (Table S14), the risk of having a full sib with AD is almost twice as high as having a full sib with SD. This difference from expectation is highly significant (p-value < $2.2x10^{-16}$), using a Binomial exact test and setting the probability of success (probability of AD) = 0.0069/ (0.0069+0.0088) =0.44. For comparison, in the cohort as a whole, the ratio of rates, AD to SD, is .78; its converse is 1.28. For all other relative types, the risk of having a relative diagnosed with AD is less than that for SD. For example, for an AD proband, on average the ratio of risk for his/her cousins (AD to SD) is roughly 0.77, very similar to that for the entire cohort.

Alternatively, when ascertaining a family through an SD proband (Table S15), an affected sibling is twice as likely to have the same diagnosis as the proband then she/he is to have a diagnosis of AD (Binomial Exact Test, p-value = $8.7x10^{-6}$). For other types of relatives, this ratio tends toward rates more consistent with the full cohort.

Notably, for cousins, the average ASD unstructured recurrence risk differs very little whether the family is accessed through an AD proband versus an SD proband: 0.029 versus 0.030. Taken together these results suggest several points consistent with an additive model. First, parents of AD probands tends to carry more risk alleles than parents of SD probands, i.e., have greater burden, which would explain why siblings of AD (SD) probands are more likely to have an AD (SD) diagnosis. Second, for more distant relatives the burden of ASD risk alleles in their parents tends to be diluted. As a result, ASD cases in relatives tend to get fewer risk alleles, leading to lower severity and a diagnosis with SD. Nonetheless, at the level of cousins, there still is a greater tendency for SD probands to have SD cousins, SD/AD = 1.82, whereas the ratio for cousins of AD probands is 1.37. This, too, is consistent with an additive model.

Table S14. ASD, AD, and SD risk for relatives of AD probands.

	Risk			Ratio of Risk
	ASD	AD	SD	AD vs SD
FS	0.1152	0.0766	0.0425	1.80
mHS	0.0792	0.0338	0.0468	0.72
pHS	0.0760	0.0233	0.0540	0.43
mPC	0.0305	0.0115	0.0197	0.58
mCC	0.0293	0.0116	0.0187	0.62
pCC	0.0300	0.0143	0.0160	0.89
pPC	0.0280	0.0134	0.0148	0.91

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Table S15. ASD, AD, and SD risk for relatives of SD probands.

	Risk			Ratio of Risk
	ASD	AD	SD	SD vs AD
FS	0.0989	0.0332	0.0683	2.06
mHS	0.0577	0.0290	0.0294	1.01
pHS	0.0589	0.0305	0.0303	0.99
mPC	0.0353	0.0125	0.0236	1.89
mCC	0.0287	0.0135	0.0158	1.17
pCC	0.0273	0.0115	0.0168	1.46
pPC	0.0305	0.0090	0.0228	2.53

Notes: FS: full sibs; mHS: maternal half sibs; pHS: paternal parallel cousins; mPC: maternal parallel cousins; mCC: maternal cross cousins; pCC: paternal cross cousins; pPC: paternal parallel cousins.

Addendum

Deviations from population patterns of risk

Deviation of risk in PHS and MHS from prevalence for ASD

Prevalence ASD=0.0151

Based on 100 samples

Risk in PHS is 0.0283 ± 0.0022, $p=1.62\times10^{-8}$ based on the t distribution with 99 df.

Risk in MHS is 0.0234 ± 0.0020, $p=3.52\times10^{-5}$ based on the t distribution with 99 df.

Deviation of risk in FS for AD versus SD

In the population, the ratio of AD vs SD cases is 43.7% to 56.3%. The AD cases have a total of 249.8 and 143.7 FS with AD and SD, respectively (partial counts are due to adjustments for family size). This is a ratio of 63.4% to 36.5%. A binomial exact test using the number of success of 249 (249.8 rounded down) out of a number of trials of 394 (249.8+143.7 rounded up) with a probability of success of 0.437 shows a p-value = 8.36×10^{-15} (two-sided). The same calculation for SD shows a total of 143.7 full siblings with AD and 287.3 with SD (33.3% vs 66.7%). The binomial exact test with inputs 287 for the number of successes, number of trial as 431 and a probability of success of 0.563 gives p-value 1.46×10^{-5}.

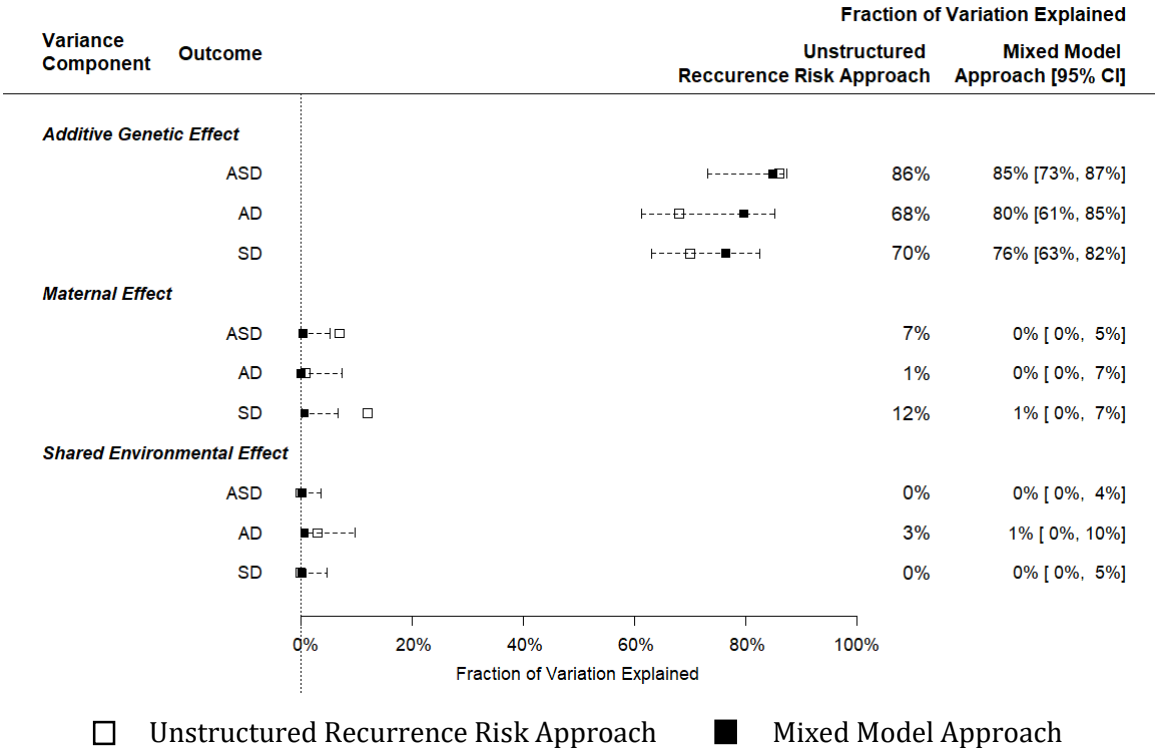

Figure S1. Fractions of Variation Explained, Unstructured Recurrence Risk Estimates vs. Mixed Model Estimates

ASD: Autism Spectrum Disorder.

AD: Autistic Disorder.

SD: Asperger and Pervasive Development Disorders Not Otherwise Specified combined.