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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDA, NCI, or the NIH.

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The Heritability of Autism Spectrum Disorder

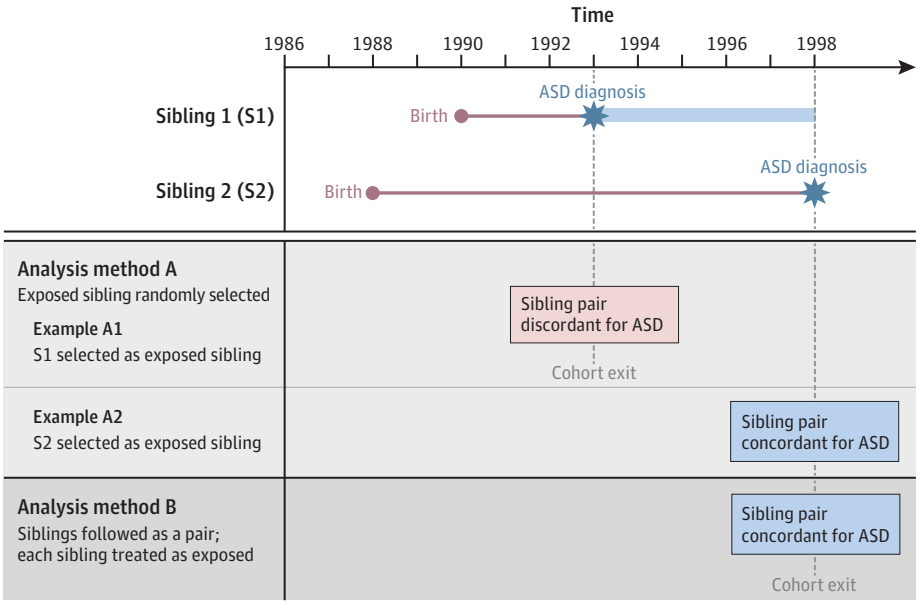
Studies have found that autism spectrum disorder (ASD) aggregates in families, and twin studies estimate the proportion of the phenotype variance due to genetic factors (heritability) to be about 90%.[1]

In a previous study,[2] ASD heritability was estimated to be 0.50, and shared familial environmental influences to be 0.04. To define presence or absence of ASD, the study used a data set created to take into account time-to-event effects in the data, which may have reduced the heritability estimates (detailed explanation in **Figure**).

Using the same underlying data as in the previous study,[2] we used an alternate method (used by previous studies in the field) to define concordant and discordant sibling pairs to calculate the heritability of ASD.

Methods | A population-based cohort of children born in Sweden 1982 through 2006, with follow-up for ASD through December 31, 2009, were included. The study population and case-ascertainment methods are described in detail elsewhere.[2] The study was approved, with a waiver of informed consent, by the ethics committee at the Karolinska Institutet.

Figure. Examples of Methods for Defining ASD-Discordant and ASD-Concordant Sibling Pairs



The concordant or discordant status of the pair is determined at the end of follow-up of the exposed sibling (cohort exit).

ASD indicates autism spectrum disorder. Each sibling is followed from birth to end of follow-up (death, emigration, or end of follow-up) or ASD diagnosis. Analysis methods A and B agree for the clear majority of all sibling pairs. If S2 was not observed with ASD, the concordance or discordance status would be the same for both methods. In the Figure, for the family with 2 siblings where S1 is diagnosed with ASD in 1993 and S2 in 1998, the sibling pair (S1, S2) will be discordant in 1993 because S2 is censored at the ASD diagnosis of S1. However, the pair (S2, S1) will be concordant in 1998. The 2 pairs are 2 candidates representing the family. For calculating heritability, 1 of these representative sibling pairs was randomly selected. As a consequence, the algorithm led to a loss of about half of the concordant pairs compared with results under the assumptions and methods applied in the alternate method (analysis method B),[3] in which calculating heritability typically does not consider sibling pairs as both discordant or concordant depending on which sibling is considered dependent, but instead follows them as a pair.

Table. Autism Spectrum Disorder Heritability Model Comparisons and Parameter Estimates

Models[b]	Model Comparison Measures: No. of Model Parameters	−2LL	Diff − 2LL	*P* Value[c]	Estimated Variance (95% CI)[a]: Additive Genetic (Narrow-Sense Heritability)	Nonadditive Genetic	Environment: Shared	Environment: Nonshared	Total Genetic (Broad-Sense Heritability)
ACDE	14	146 836	NA	NA	0.69 (0.40-0.86)	0.10 (0.00-0.38)	0.04 (0.00-0.14)	0.16 (0.05-0.30)	0.80 (0.59-0.95)
ACE	13	146 836	0.4	.52	0.77 (0.58-0.87)	NA	0.03 (0.00-0.13)	0.20 (0.13-0.30)	0.77 (0.58-0.87)
ADE	13	146 836	0.8	.38	0.80 (0.68-0.87)	0.05 (0.00-0.26)	NA	0.15 (0.05-0.21)	0.85 (0.79-0.95)
CDE	13	146 856	20.9	<.001	NA	0.64 (0.48-0.75)	0.25 (0.21-0.29)	0.11 (0.03-0.24)	0.64 (0.48-0.75)
AE	12	146 836	0.9	.64	0.83 (0.79-0.87)	NA	NA	0.17 (0.13-0.21)	0.83 (0.79-0.87)
DE	12	147 100	264	<.001	NA	0.99 (0.97-1.00)	NA	0.01 (0.00-0.03)	0.99 (0.97-1.00)
CE	12	146 897	61	<.001	NA	NA	0.39 (0.37-0.41)	0.61 (0.59-0.63)	NA
E	11	147 996	1160	<.001	NA	NA	NA	1.00 (1.00-1.00)	NA

Abbreviations: 2LL, 2 × logarithm of the likelihood; Diff − 2LL, 2 × difference in log-likelihood between the model and the full model; NA, not applicable.

[a] The 95% CIs are 2-sided CIs. Variances are based on the tetrachoric correlations. The unadjusted tetrachoric correlation (SD) was estimated to 0.87 (0.08) and 0.40 (0.10) for monozygotic and dizygotic twins; 0.41 (0.01) for full siblings; 0.22 (0.03) and 0.17 (0.04) for maternal and paternal half siblings.

[b] All models adjusted for sex and birth cohort. The genetic terms for each model are shown in each row, which include additive genetic effect (A; inherited additive effects of different alleles), shared environmental factors (C; nongenetic influences contributing to similarity within sibling pairs), nonadditive (dominant) genetic factors (D; interaction effects between alleles at the same locus), and nonshared environmental factors (E; making siblings dissimilar).

[c] *P* value for testing the hypothesis: the parameters not in the model but in the full model are all equal to 0.

Liability-threshold models were fitted using monozygotic or dizygotic twins, full siblings, and paternal and maternal half siblings to decompose the variance in liability to ASD into factors for additive genetic effect (inherited additive effects of different alleles), nonadditive (dominant) genetic factors (interaction effects between alleles at the same locus), shared environmental factors (nongenetic influences contributing to similarity within sibling pairs), and nonshared environmental factors (making siblings dissimilar).[3] From each family, 1 sibling pair was randomly included. For each pair, ASD status was defined as the presence or absence of ASD at any time point during follow-up. Differences in probability of being diagnosed depended on birth cohort, due to differing time of follow-up and changes in diagnostic practices, and were handled by adjustment for birth year. Models obtained by excluding 1 or more of the 4 genetic and environmental parameters were compared using likelihood ratio tests. The heritability was calculated as the variance associated with the genetic term(s) divided by the total variance. A 2-sided *P* value of less than .05 was the threshold for statistical significance. Models were fitted using OpenMx (OpenMx Project), version 2.6.9, and R (R Foundation), version 3.3.3.

Results | The study included 37 570 twin pairs, 2 642 064 full sibling pairs, and 432 281 maternal and 445 531 paternal half-sibling pairs. Of these, 14 516 children were diagnosed with ASD. The model including additive and nonadditive genetic, shared and nonshared environmental parameters was chosen as the full model under which nested submodels were tested. The best-fitting model included only additive genetic and nonshared environmental parameters (**Table**). Using this model, the ASD heritability was estimated as 0.83 (95% CI, 0.79-0.87) and the nonshared environmental influence was estimated as 0.17 (95% CI, 0.13-0.21). In the full model, the shared environment variance was estimated as 0.04 (95% CI, 0.00-0.14); nonshared environment, 0.16 (95% CI, 0.05-0.30); nonadditive genetic, 0.10 (95% CI, 0.00-0.38); and additive genetic (heritability), 0.69 (95% CI, 0.40-0.86). Using only twins, the heritability was estimated as 0.87 (95% CI, 0.68-0.96).

Discussion | In a reanalysis of a previous study of the familial risk of ASD, the heritability was estimated to be 83%, suggesting that genetic factors may explain most of the risk for ASD. This estimate is slightly lower than the approximately 90% estimate reported in earlier twin studies[1] and higher than the 38% (95% CI, 14%-67%) estimate reported in a California twin study,[4] but was estimated with higher precision. Like earlier twin studies, shared environmental factors contributed minimally to the risk of ASD.

Twin and family methods for calculating heritability require several, often untestable assumptions.[5,6] Because ASD is rare, estimates of heritability rely on few families with more than 1 affected child, and, coupled with the time trends in ASD prevalence, the heritability estimates are sensitive to the choice of methods. The method initially chosen in the previous study[2] led to a lower estimate of heritability of ASD. The current estimate, using traditional methods for defining ASD discordance and concordance, more accurately captures the role of the genetic factors in ASD. However, in both analyses, the heritability of ASD was high and the risk of ASD increased with increasing genetic relatedness.

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Drafting of the manuscript: Sandin, Hultman, Reichenberg.
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COMMENT & RESPONSE

Long-term Intra-articular Steroid Injections and Knee Cartilage

To the Editor Dr McAlindon and colleagues investigated the long-term effects on cartilage of intra-articular corticosteroid injections in the knee every 3 months for 2 years in people with knee osteoarthritis.[1] With respect to the clinical outcome, we agree with the authors that the usual short-term benefits after the injections probably were missed.

The repeated injections were given independent of the severity of symptoms and the presence of inflammatory signs, and results of this study indicate that such repeated injections can have deleterious effects on the cartilage after 2 years. It would be interesting to know if these effects were present in patients with inflammatory signs at each repeated injection, severe knee pain, or a flare of pain, which are the usual indications for such injections in clinical practice.

The change in cartilage volume was defined as the primary structural outcome in the trial register and study protocol. Also, the sample size calculation was based on the detection of a difference in cartilage volume of 90 mm^3 between the groups. The operationalization of this cartilage volume measure was not mentioned in the original study protocol, trial register, or the sample size calculation reported in the article. Moreover, the standard deviation of 224 mm^3 in the sample size calculation cannot be found in the article the authors cited.[2] The treatment difference used in the sample size calculation suggests that the proxy total cartilage damage index may have been used. However, in the analytic plan, the authors reported that they used cartilage thickness as a proxy for cartilage volume. Moreover, in the final analysis plan (undated) provided in the supplement, the authors stated that they had used as the primary outcome the cartilage damage index and the mean cartilage thickness. In summary, we are confused about what the original primary structural outcome was in this study. If it was the total cartilage damage index, no statistically significant difference was found between the groups (Table 2 in the article), which might change the conclusion.

It would be of interest to know whether for any of the structural outcome measures used in this study the predictive value with respect to clinical decline is known and whether the differences reported are large enough to affect future clinical decline.

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1. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA*. 2017;317(19):1967-1975.

2. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA*. 2013;309(2):155-162.

To the Editor The randomized clinical trial by Dr McAlindon and colleagues[1] evaluated intra-articular administration of triamcinolone in the knee every 3 months. It is not surprising that clinical benefit 3 months following injection relative to placebo was not observed. The analgesic effect following corticosteroid injection is limited to weeks in duration.[2]

Corticosteroid injections, indicated for acute, symptomatic episodes of pain, are not commonly repeated at 3-month intervals. The use of an intervention that is not consistent with clinical practice raises questions about the validity and generalizability of the study. Presumably, the authors chose this regimen with the hope of providing beneficial effects on joint structure and patient symptoms. The