JAMA Psychiatry | Original Investigation

Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort

Dan Bai, MSc; Benjamin Hon Kei Yip, PhD; Gayle C. Windham, PhD, MSPH; Andre Sourander, PhD; Richard Francis, PhD; Rinat Yoffe, MPH; Emma Glasson, PhD; Behrang Mahjani, PhD; Auli Suominen, MSc; Helen Leonard, MBChB, MPH; Mika Gissler, PhD; Joseph D. Buxbaum, PhD; Kingsley Wong, PhD; Diana Schendel, PhD; Arad Kodesh, MD; Michaeline Breshnahan, PhD, MPH; Stephen Z. Levine, PhD; Erik T. Parner, PhD; Stefan N. Hansen, PhD; Christina Hultman, PhD; Abraham Reichenberg, PhD; Sven Sandin, PhD

IMPORTANCE The origins and development of autism spectrum disorder (ASD) remain unresolved. No individual-level study has provided estimates of additive genetic, maternal, and environmental effects in ASD across several countries.

OBJECTIVE To estimate the additive genetic, maternal, and environmental effects in ASD.

DESIGN, SETTING, AND PARTICIPANTS Population-based, multinational cohort study including full birth cohorts of children from Denmark, Finland, Sweden, Israel, and Western Australia born between January 1, 1998, and December 31, 2011, and followed up to age 16 years. Data were analyzed from September 23, 2016 through February 4, 2018.

MAIN OUTCOMES AND MEASURES Across 5 countries, models were fitted to estimate variance components describing the total variance in risk for ASD occurrence owing to additive genetics, maternal, and shared and nonshared environmental effects.

RESULTS The analytic sample included 2 001 631 individuals, of whom 1 027 546 (51.3%) were male. Among the entire sample, 22 156 were diagnosed with ASD. The median (95% CI) ASD heritability was 80.8% (73.2%-85.5%) for country-specific point estimates, ranging from 50.9% (25.1%-75.6%) (Finland) to 86.8% (69.8%-100.0%) (Israel). For the Nordic countries combined, heritability estimates ranged from 81.2% (73.9%-85.3%) to 82.7% (79.1%-86.0%). Maternal effect was estimated to range from 0.4% to 1.6%. Estimates of genetic, maternal, and environmental effects for autistic disorder were similar with ASD.

CONCLUSIONS AND RELEVANCE Based on population data from 5 countries, the heritability of ASD was estimated to be approximately 80%, indicating that the variation in ASD occurrence in the population is mostly owing to inherited genetic influences, with no support for contribution from maternal effects. The results suggest possible modest differences in the sources of ASD risk between countries.

Editorial page 1005

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sven Sandin, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 6, SE-17177 Stockholm, Sweden (sven.sandin@ki.se).

JAMA Psychiatry. 2019;76(10):1035-1043. doi:10.1001/jamapsychiatry.2019.1411
Published online July 17, 2019.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication and the presence of restricted interests and repetitive behaviors.[1,2]

Autism spectrum disorder has both genetic and environmental origins. Research into the genetic origins of ASD has consistently implicated common and rare inherited variation (heritability). However, evidence shows that there are other, noninherited, genetic influences that could be associated with variation in a trait.[3] Given the prenatal origins of ASD, an important source of such genetic influences could be maternal effects.[4] The term *maternal effects* is used to describe the association of a maternal phenotype with ASD in offspring (ie, the noninherited genetic influences originating from mothers beyond what is inherited by the offspring). Maternal effects have been associated with a substantial proportion of the variation in several traits associated with ASD, including preterm birth[5] and intelligence quotient.[6] Research on nongenetic origins has frequently pointed to a role for environmental exposures unique to different family members (nonshared environment), an example of which is cesarean delivery.[7] In contrast, contribution from environmental exposures that make family members similar (ie, shared environment), has been uncertain.[8]

A meta-analysis of twin studies estimated heritability to be in the range of 64% to 91%,[8] and 3 population-based studies from Sweden recently estimated the heritability of ASD to be 83%,[9] 80%,[4] and 66%.[10] Among those earlier heritability calculations from twin and family studies (eTable 1 in the Supplement), a single study has estimated maternal effects,[4] reporting modest, if any, contribution to ASD. Estimates of the contribution of shared environment range from 7% to 35%,[8] but multiple studies estimate the contribution to be zero.[4,9,11,12] Thus, although the origin and development of ASD has been investigated for half a century, it remains controversial.

The current study was designed to rigorously determine the contribution of various genetic and nongenetic origins hypothesized for ASD. We aimed to estimate the heritability together with maternal effects and shared and nonshared environmental effects of ASD. To achieve this aim, we used what is to our knowledge the largest-ever dataset for population-based epidemiologic autism research to date containing family data from 5 countries and generalized linear mixed models designed to quantify the variation in ASD liability owing to genetic and environmental origins using information about ASD in family members of varying levels of relatedness (eg, siblings, cousins).[4] We aimed to examine the consistency of these estimates by contrasting the results across 5 different countries. Data were analyzed for each country and in an individual-level pooled analysis for Nordic countries to maximize precision.

Key Points

Question What are the etiological origins of autism spectrum disorder?

Findings In a large population-based multinational cohort study including more than 2 million individuals, 22 156 of whom were diagnosed with ASD, the heritability of autism spectrum disorder was estimated to be approximately 80%, with possible modest differences in the sources of autism spectrum disorder risk replicated across countries.

Meaning The variation in the occurrence of autism spectrum disorder in the population is mostly owing to inherited genetic influences, with no support for contribution from maternal effects.

Methods

This study was approved by the Danish Data Protection Agency, the Danish National Board of Health, the institutional review boards of the University of Haifa and the Helsinki Ethics Committee, the ethics committee of the Finnish National Institute for Health and Welfare and hospital district of Southwest Finland, the Swedish Ethical Review Board Stockholm, the Department of Health Western Australia Human Research Ethics Committee, and the Institutional Review Board of the New York State Psychiatric Institute. Those bodies waived the need for informed consent because the study data were fully deidentified.

Study Population

The study population comprised all singleton live births in Denmark, Finland, Sweden, Israel, and Western Australia. For Denmark, Sweden, Finland, and Western Australia, we included all births between January 1, 1998, and December 31, 2007 (eAppendix 1 in the Supplement). For Israel, we included all births between January 1, 2000, and December 31, 2011, from offspring of an established cohort (eAppendix 2 in the Supplement).[13] Multiple births were excluded because no information about zygosity was available. Individuals were followed for a diagnosis of ASD from birth up to December 31, 2014, in Sweden; December 31, 2013, in Denmark; December 31, 2012, in Finland; December 31, 2014, in Israel; and July 1, 2011, in Western Australia. Data on 3-generational family linkages, allowing for the identification of parents, siblings, and cousins, were available for all sites (eTable 2 in the Supplement). Data were analyzed from September 23, 2016, to February 4, 2018.

Outcome and Covariates Information

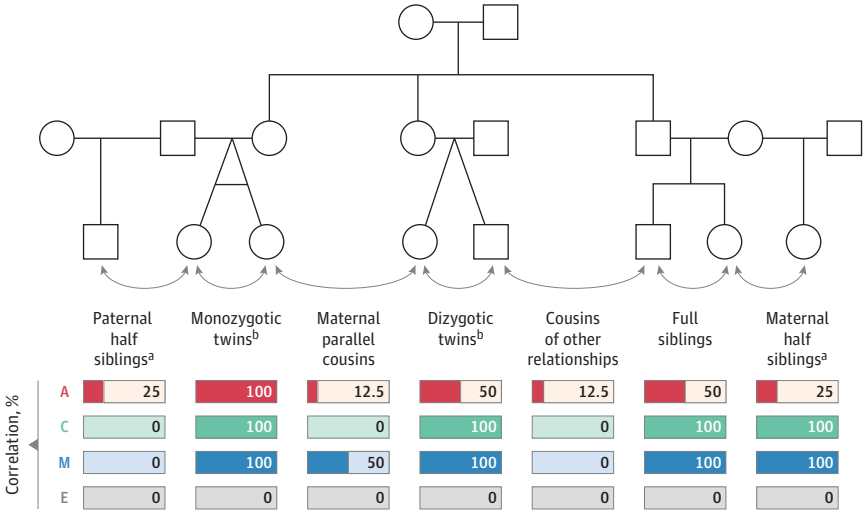
Outcome and covariate information (birth year, sex) were provided by government-maintained national health registries.[14] Different diagnostic systems were used across sites (eTable 2 in the Supplement) and the diagnostic codes for ASD were harmonized accordingly (eTable 3 in the Supplement). Data from Israel were only used for ASD analyses because autistic disorder (AD) diagnosis was not available. Case ascertainment and reliability and validity of registry-reported diagnoses have been published previously.[15,16]

Statistical Analysis

Analytic Samples and Statistical Models

We chose a multigenerational family design because the strength of genetically induced correlation for a given trait varies by the degree of relatedness between relatives, which allows additive

Figure 1. Variance Component Derivation From Correlations Between Family Members



Circles represent female and squares represent male family members. Curved arrows indicate family relationships used in the calculations. A indicates additive genetic effect; C, shared environmental effect; E, nonshared environmental effect; M, maternal effect; and mPCs, maternal parallel cousins.

[a] Half siblings were excluded from the main analysis based on the assumption on shared environmental effect, which assumes children always live with their mother, and all 4 variance components can be estimated with full siblings and cousins (mPCs and cousins of other relationships).

[b] Twins were excluded from the present study owing to lack of information about zygosity status.

genetic (heritability), maternal, and shared environmental effects to be estimated. A residual term, which is commonly interpreted as nonshared environmental effects, can also be estimated.[17] Thus, nonshared environment will not be an estimate of nonshared environmental effects only but will also include contributions from sources not explicitly represented by any model parameters, including gene-environmental correlations and part(s) of any gene-environmental interactions. We chose to use the term *nonshared environment* for this term to not diverge from earlier publications in this field. The data preparation and modeling approach has been described in detail elsewhere[4] (eAppendix 2 in the Supplement). Briefly, we used the 3-generational data sources to construct families that vary by genetic relatedness and therefore are informative for genetic modeling. These included full siblings and cousins related through their mothers (maternal parallel cousins [mPCs]), or cousins of other relationships. Detailed examples illustrating how families were created are provided in eFigure 1 through eFigure 5 in the Supplement.

Liability threshold models were fitted using the structured family data to decompose the variance in liability to ASD into additive genetic (A), maternal (M), and shared (C) and nonshared (E) environmental components. Three nested models were fitted: (1) the AE model: additive genetic (A) + nonshared environment (E); (2) the ACE model: additive genetic (A) + shared environment (C) + nonshared environment (E); and (3) the ACME model: additive genetic (A) + shared environment (C) + maternal effect (M) + nonshared environment (E). **Figure 1** and eTable 4 in the Supplement show how the different components of variance are derived from different correlations between family members representing additive genetic, shared environment, and nonshared environment. These components can be derived from twins (monozygotic vs dizygotic); full siblings vs half siblings; and full siblings vs cousins. The M component can only be derived from full siblings vs mPCs vs cousins of other relationships and full siblings vs maternal vs paternal half siblings. When involving half siblings, correlation of shared environmental effect was set at 1 for maternal half siblings and 0 for paternal half siblings; an assumption behind this decision is that children lived with their mothers after a divorce and separation from the father, an assumption frequently made in these types of models; this is also the rationale for excluding half siblings in our analytic sample. Liability models using full siblings and cousins to estimate A, C, and E have been used earlier and for other outcomes (eg, skin cancer,[18,19] M component on preterm birth[5] and preeclampsia,[20,21] and comorbidity of 2 diseases).[22] To calculate CIs, instead of relying on the assumption that estimates follow an asymptotic normal distribution, we calculated 2-sided 95% CIs using profile likelihood methods.[23]

Because Denmark, Finland, and Sweden share similar health, ascertainment, and diagnostic systems, and because of sample size considerations, the primary pooled analysis focused on the Danish, Finnish, and Swedish samples. First, we fitted country-specific models for Denmark, Finland, and Sweden. Then, a model was fitted for the individual-level combined data from Nordic countries. Next, we included 2 smaller samples from Israel and Western Australia. For each country, the categorical covariates sex (male vs female) and birth year cohort (2006-2011 vs 2000-2005 for Israel and 2003-2007 vs 1998-2002 for all other countries) were included as fixed factors.

We used the ViPAR[24] application running R statistical software[25] version 3.1.2 (R Foundation) on a Linux RedHat version 6.0 64-bit server (Hewlett Packard) or all calculations except for Israel, for which we used R version 3.4.0 on a Linux/GNU 64-bit server through Ubuntu 16.04 (Canonical Ltd). Further details about the choice of statistical software and analysis packages are provided in eAppendix 2 in the Supplement. All tests of statistical hypotheses were done on a 2-sided 5% level of significance.

Sensitivity and Complementary Analyses

To delineate a more impaired subtype within ASD, we repeated all analyses for AD, a diagnostic category present in the ninth and tenth revisions of the *International Classification of*

Table 1. Outcomes and Characteristics of the Analytic Sample

Outcome	Countries					Total
	Denmark	Finland	Sweden	Israel	Western Australia	
Families, No.[a]	183 034	160 570	262 047	37 430	37 421	680 502
Children, No.[b]	528 052	472 959	753 125	131 147	116 348	2 001 631
Sex, No.						
Male	270 844	241 909	388 126	67 237	59 430	1 027 546
Birth cohort						
1998-2002	270 564	240 984	360 351	75 220[c]	57 822	974 085
2003-2007	257 488	231 975	392 774	55 927[d]	58 526	929 721
ASD cases, No.	7580	2968	10 563	490	555	22 156
AD cases, No.	2676	709	4303	NA	459	8147
Asperger syndrome, No.	1731	1044	3557	NA	7	6339
PDD-NOS	3173	1215	2703	NA	89	7180
Children, No.						
Cousins[e]	467 836	404 410	652 803	113 851	109 550	1 748 450
mPCs[f]	119 257	104 218	168 524	25 052	28 899	445 950
Full siblings[g]	355 099	330 948	518 762	106 893	80 394	1 392 096
ASD concordance pairs, No.						
Cousins	99	10	121	4	2	236
mPCs	30	3	33	3	1	70
Full siblings	191	69	353	7	19	639

Abbreviations: AD, autistic disorder; ASD, autism spectrum disorder; mPCs, maternal parallel cousins; NA, not available; PDD-NOS, pervasive developmental disorder not otherwise specified.

[a] Data were organized in unit of family based on relatedness type in the Methods section.

[b] Owing to data structure requirement by the statistical modeling, replicates exist (eAppendix 2: Analytic Sample Ascertainment in the Supplement).

[c] Birth cohort 2000-2005.

[d] Birth cohort 2006-2011.

[e] Cousins are defined as children (cousins and full siblings) in the paired cousin families.

[f] mPCs is defined as children (cousins and full siblings) in the families based on maternal parallel cousin pairs.

[g] Full siblings are defined as full siblings from all 4 types of families defined based on relatedness.

Diseases, Ninth Revision, Clinical Modification and the revised third and the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. In addition, we performed an extensive set of analyses to test the robustness of our results. We performed 3 sensitivity analyses. For Finland and Western Australia, which had a small number of concordance pairs, we refitted the ACE model using half siblings instead of cousins. Because a lower prevalence could affect the heritability estimates, we used data simulation reducing the number of ASD cases in the Swedish analytic sample to approximate prevalence rates in Finland and refitted the ACE model. To illustrate the model robustness, we plotted the country-specific likelihood functions of additive genetic (A) and shared environmental (C) effect for the ACE models. To test the robustness of our results, because the analytic sample used for the statistical models did not include the entire study cohort, we performed additional analyses to ensure that the analytic sample was representative of the study cohort. We also compared age-specific outcome ascertainment and follow-up pattern between countries by constructing country-specific inverse Kaplan-Meier curves for ASD and AD assuming independent censoring (eAppendix 3 in the Supplement).

Results

The analytic sample included 2 001 631 children, of whom 1 027 546 (51.3%) were male, from 680 502 families followed up to age 16 years. Of these, 22 156 (1.11%) children were diagnosed with ASD (Denmark, 7580; Finland, 2968; Sweden, 10 563; Israel, 490; Western Australia, 555) (**Table 1**). Outcome ascertainment information across sites can be found in eTable 2 and eTable 3 in the Supplement, which provide information about the diagnostic codes used by the different countries; eTable 9 provides information about the underlying population from which we selected the analytic sample used in the calculations.

Nordic Countries: Country-Specific and Combined Estimates

Country-specific point estimates of additive genetic effect (narrow-sense heritability) ranged between 80.7% (95% CI, 74.1%-85.4%) (Denmark) and 84.1% (95% CI, 79.7%-88.1%) (Sweden) for the AE model; 52.8% (95% CI, 29.7%-76.3%) (Finland) and 84.8% (95% CI, 76.2%-88.7%) (Sweden) for the ACE model; and 50.9% (95% CI, 25.1%-75.6%) (Finland) and 81.1% (95% CI, 69.9%-86.7%) (Sweden) for the ACME model. The heritability estimates for the Nordic pooled sample were 82.7% (95% CI, 79.1%-86.0%) for the AE, 82.2% (77.2%-85.9%) for the ACE model, and 81.2% (95% CI, 73.9%-85.3%) for the ACME model (**Table 2**; **Figure 2**).

Country-specific point estimates of maternal effects ranged between 0.4% and 1.6% in the ACME model, and the Nordic pooled sample estimate was 0.5%, but in all models the 2-sided 95% CIs included zero (Table 2; eFigure 12 in the Supplement).

Country-specific point estimates of shared environmental effects ranged between 0.0% (95% CI, 0.0%-4.6%) (Den-

Table 2. Autism Spectrum Disorder: Estimated Variance Components[a] and Associated 2-Sided 95% CI for Denmark, Finland, Sweden, and Nordic Countries Combined[b]

Model and Population	Random Effects (95% CI)			
	Additive Genetic (A)	Shared Environment (C)	Maternal (M)	Nonshared Environment (E)
Model 1: A + E				
Country specific				
Denmark	80.7 (74.1-85.4)	NA	NA	19.3 (14.6-25.9)
Finland	80.8 (73.2-85.5)	NA	NA	19.2 (14.5-26.8)
Sweden	84.1 (79.7-88.1)	NA	NA	16.0 (11.9-20.4)
Nordic countries combined	82.7 (79.1-86.0)	NA	NA	17.3 (14.0-20.9)
Model 2: A + C + E				
Country specific				
Denmark	80.4 (71.3-86.8)	0.0 (0.0-4.6)	NA	19.6 (12.9-25.3)
Finland	52.8 (29.7-76.3)	14.5 (4.5-29.2)	NA	32.8 (17.6-51.1)
Sweden	84.8 (76.2-88.7)	0.1 (0.0-3.4)	NA	15.1 (11.1-21.1)
Nordic countries combined	82.2 (77.2-85.9)	0.2 (0.0-2.3)	NA	17.7 (13.9-26.5)
Model 3: A + C + M + E				
Country specific				
Denmark	78.9 (65.4-84.3)	0.1 (0.0-4.8)	0.4 (0.0-6.9)	20.6 (14.6-26.5)
Finland	50.9 (25.1-75.6)	14.0 (0.0-28.6)	1.6 (0.0-13.4)	33.6 (17.6-53.9)
Sweden	81.1 (69.9-86.7)	0.0 (0.0-3.7)	1.4 (0.0-6.6)	17.5 (12.5-22.5)
Nordic countries combined	81.2 (73.9-85.3)	0.3 (0.0-2.2)	0.5 (0.0-3.5)	18.1 (14.1-21.7)

Abbreviation: NA, not applicable.

[a] All estimates are recalculated to fraction of variation explained, the proportion of total variance explained by each random effect (eAppendix 2 in the Supplement).

[b] Nordic countries combined are Denmark, Finland, and Sweden.

mark) and 14.5% (95% CI, 4.5%-29.2%) (Denmark) in the ACE model and 0.0% (95% CI, 0.0%-3.7%) (Sweden) and 14.0% (95% CI, 0.0%-28.6%) (Finland) in the ACME model. The estimates from the Nordic pooled sample ranged between 0.2% (95% CI, 0.0%-2.3%) for the ACE and 0.3% (95% CI, 0.0%-2.2%) for the ACME model; CIs included zero (Table 2; eFigure 12 in the Supplement).

Country-specific point estimates for nonshared environmental effects ranged between 16.0% (95% CI, 11.9%-20.4%) (Sweden) and 19.3% (95% CI, 14.6%-25.9%) (Denmark) in the AE model; 15.1% (95% CI, 11.1%-21.1%) (Sweden) and 32.8% (95% CI, 17.6%-51.1%) (Finland) in the ACE model; and 17.5% (95% CI, 12.5%-22.5%) (Sweden); and 33.6% (95% CI, 17.6%-53.9%) (Finland) for the ACME model. The Nordic pooled sample estimates were 17.3% (95% CI, 14.0%-20.9%) for the AE model; 17.7% (95% CI, 13.9%-26.5%) for the ACE model; and 18.1% (95% CI, 14.1%-21.7%) for the ACME model (Table 2; eFigure 13 in the Supplement).

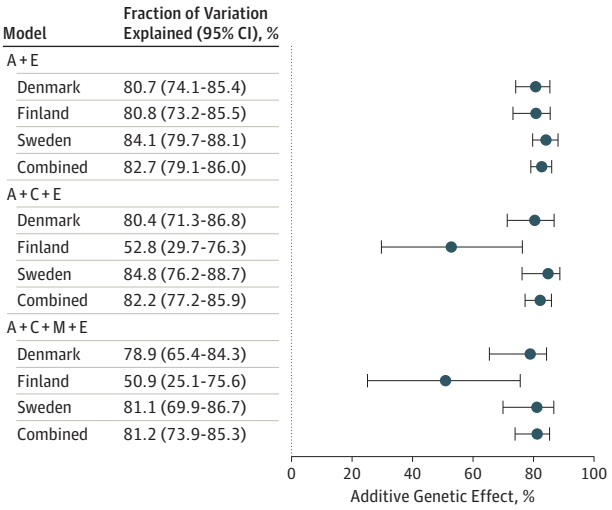
Israel and Western Australia

Owing to sample size limitations for Israel and Western Australia, only the ACE model could be fitted for these 2 countries. Results for Israel for additive genetic effect (86.8% [95% CI, 69.8%-100.0%]) were similar to those from Denmark and Sweden, whereas results from Western Australia resembled those from Finland (additive genetic effect 53.8% [28.5%, 74.3%]) (**Table 3**; eFigure 6 in the Supplement).

Sensitivity Analyses

Because Finland and Western Australia showed reduced heritability estimates and an increased contribution from shared environment to ASD compared with the remaining countries (Table 2, eFigure 6 in the Supplement), we executed a series of sensitivity analyses. Finland and Western Australia had a small number of concordant cousin pairs, and we therefore refitted the ACE model using half siblings instead of cousins. The

Figure 2. Autism Spectrum Disorder (ASD): Estimated Shared Environmental and Maternal Effect (2-Sided 95% CI) for Denmark, Finland, Sweden, and Nordic Countries Combined



All estimates are recalculated to fraction of variation explained. A indicates additive genetic effect; C, shared environmental effect; E, nonshared environmental effect; and M, maternal effect.

Table 3. Autism Spectrum Disorder: Estimated Variance Components[a] and Associated 2-Sided 95% CIs for Israel and Western Australia

Population	Random Effects (95% CI), % for Model 2: A + C + E		
	Additive Genetic (A)	Shared Environment (C)	Nonshared Environment (E)
Israel	86.8 (69.8-100.0)	0.1 (0.0-5.4)	13.1 (10.9-18.8)
Western Australia	53.8 (28.5-74.3)	25.2 (8.6-49.2)	21.0 (13.2-36.0)

[a] All estimates are recalculated to fraction of variation explained, the proportion of total variance explained by each random effect (eAppendix 2 in the Supplement).

estimates from the ACE model for Finland and Western Australia using this approach were more similar to those observed for the other countries. For example, for Finland, heritability was estimated to 70.6%; shared environment estimated, 9.4%; and nonshared environment, 20.0% (eTable 5 in the Supplement).

Using a simulation approach, we reduced the Swedish ASD prevalence to approximate the level in Finland (Sweden simulation: 6.91 ASD cases per 1000 vs Finland, 6.89 cases per 1000). The heritability estimate from this simulation was more similar to that of Finland (simulation: 62.0% [95% CI, 54.1%-70.9%] vs Finland above, 50.9% [95% CI, 25.1%-75.6%]), but the shared environmental effect was 0.7% (95% CI, 0.0%-6.8%) compared with Finland (14.0% [95% CI, 0.0%-28.6%]) (eTable 6 in the Supplement). Taken together, the sensitivity analyses indicate that a random underascertainment of cases may underestimate the true heritability and increase the observed shared environment component. This is also reflected in the cumulative probability for diagnosis. Denmark and Sweden both have similar increasing cumulative probability of ASD and AD up to age 16 years, whereas the ascertainment in Western Australia and Finland is predominantly at younger ages (ASD, eFigure 10 in the Supplement; AD, eFigure 11 in the Supplement).

Complementary Analyses

We estimated genetic and environmental contributions to AD for Denmark, Finland, and Sweden. The Western Australian sample was too small, and Israel reported ASD without subtypes. Estimates of genetic, maternal, and environmental effects were similar with ASD; additive genetic effect, ACE model: 84.6% (95% CI, 69.7%-88.7%) (Denmark), 72.7% (95% CI, 54.2%-81.0%) (Finland), 76.3% (95% CI, 62.3%-83.0%) (Sweden); maternal effects for the Nordic combined sample, 0.6% (95% CI, 0.0%-4.9%), and nonshared environment ACE model, 15.1% (95% CI, 10.6%-21.5%) (Denmark), 16.7% (95% CI, 13.0%-24.5%) (Finland), 21.9% (95% CI, 16.0%-30.6%) (Sweden) (eTable 7, eTable 8, eFigure 7, eFigure 14, and eFigure 15 in the Supplement).

Demographic and clinical characteristics of the analytic cohort were representative of the corresponding populations (Table 1 vs eTable 9 in the Supplement). By visual inspection, (eFigure 8 and eFigure 9 in the Supplement), there were no differences in ASD to AD rate (cases per 1000) between the cohort population and the analytic sample. Similarly, comparisons did not reveal any differences between siblings and cousins with respect to parental age, interpregnancy interval, parental education, or parental psychiatric history (eTable 10 in the Supplement). In the analytic sample, comparisons across countries showed that siblings and cousins were similar with respect to sex ratio, AD proportion (percentage of ASD), family size, and differences in age between sibling or cousin pairs (eTable 11 in the Supplement).

All estimates of variance components were recalculated to fraction of variation explained for comparison across countries, because a number of raw estimates were associated with factors such as sample size and outcome rate (eTable 12 and eTable 13 in the Supplement). The plotted likelihood functions for the ACE model show the support in the data for estimating the variance components and the 2-sided 95% CIs (eFigure 16 in the Supplement). Estimates of fixed parameters, sex, and birth cohort for country-specific analyses and country (Denmark as reference) for the combined analyses are reported for the ACE model, which is applicable for all countries (eTable 14 and eTable 15 in the Supplement).

Discussion

The present study evaluated the contribution of various genetic and nongenetic factors to ASD risk. We estimated heritability together with maternal effects and shared and nonshared environment on ASD risk using population-based datasets from 5 countries from what is to our knowledge the largest family-based database for autism research to date. The current study results provide the strongest evidence to our knowledge to date that the majority of risk for ASD is from genetic factors. Nonshared environmental factors also consistently contribute to risk. In the models that combined data from the 3 Nordic countries, the genetic factors explained at least 73.9 % of the variability in risk, and nonshared environment at most 26.5% based on the lower and upper bounds of the respective 95% CIs. These results are similar to those of recent population-based cohorts[4,9,10] as well as a recent meta-analysis of twin studies,[8] which estimated heritability in the range of 64% to 91%.

When we estimated the maternal effect, however, its association with variation in risk for ASD (and AD) was nonexistent or minimal. This corroborates a previous analysis of the data from Sweden.[4] The importance of this finding lies in the insight it provides for understanding the risk factors associated with ASD. The absence of M effects indicates that there is no strong evidence of a maternal effect, driven by genetic factors shared between sisters, associated with the risk of ASD. Proposed maternal risk factors for ASD such as obesity[7,26,27] do not map directly to components in the current model. The mechanisms through which such risk factors operate can be better understood using other study designs and analytic approaches, including animal models and epidemiologic studies examining specific risk factors.

Like most studies,[8,11] overall shared environmental factors contributed minimally to the risk of ASD. However, there was variation in the results among samples. Although the 2 largest samples (Denmark, Sweden) did not support shared environmental influences, 2 other samples (Finland, Western Australia) did. Some variation is expected owing to population-level differences.[28] Shared environmental factors in this study may reflect variables or processes that make members of the same family similar beyond genetic factors. Indeed, studies have suggested differences in genetic population structure between Finland and the rest of Europe,[29,30] which could partially explain the increased shared environment and decreased heritability estimates for ASD in Finland. In addition, the statistical models are sensitive to small sample sizes because they rely on differences in the rate of concordant sibling-cousin pairs to estimate the shared environment component, as demonstrated in our sensitivity analyses. Bias owing to small sample size, ascertainment bias, or both, could lead to elevated estimates of shared environmental effect.

In the bulk of the analyses, results for AD and ASD were similar: additive genetic effects accounted for the largest influence on liability, followed by contribution from nonshared environment, with little evidence for maternal or shared environment effects. The pooled estimates for ASD were the same as for AD. Results for Israel were similar to those from Denmark and Sweden, whereas results from Western Australia resembled those from Finland. We believe that these patterns of results add support to the hypothesis that severity maps onto the load of liability factors.[4] Autistic disorder was part of the 9th and 10th revisions of the *International Classification of Diseases* and the revised 3rd and the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* coding system used for diagnoses in this study but is not part of the current *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, which does not separate ASD and AD.

The major strength of this study is the use of multiple large population-based samples with individual-level data in 3-generation pedigrees. Our data were based on prospective follow-up and health systems with equal access. This approach, following all participants from birth using population registers, avoids bias owing to self-report and retrospective collection of data and reduces selection biases owing to disease status or factors such as parental education. In addition to providing exceptional statistical power, the study directly addresses the concern of lack of replication in research findings[31,32] replicating results across 5 countries and health systems.

Most ASD heritability studies have used twins.[8] Although twins are important for etiological studies, also including non-twin siblings provide greater generalizability and simultaneously improve precision. A study from Sweden[9,33] used twins as well as full siblings and maternal and paternal half siblings. In a later study,[4] with data overlapping with the current Swedish sample, this approach was extended to include cousins. In the current study, we now also distinguish maternal parallel cousins from cousins of other relationships to estimate maternal effects. Twin studies rely on very specific assumptions about genetic and environmental correlations. Applying different study designs make results less sensitive to these crucial assumptions. There are also different statistical techniques to estimate the underlying (likelihood-based) models. Some studies[8,9,33] used structural equation models, others used likelihood estimation[4,5,20] or calculated tetrachoric correlations.[9,10] These methods and approaches come with their own strengths and limitations, but taken together they provide a more robust description of the underlying factors. Finally, there are also approaches using genetic markers (single-nucleotide polymorphisms) to estimate heritability.[10,34] Although these make a valuable contribution, currently they provide only a lower bound for heritability.[35] Furthermore, multiple studies have used questionnaire-based symptom checklists. Using contemporary clinical diagnoses adds to generalizability and helps to avoid biases that could be embedded in subclinical diagnoses. Finally, most previous heritability studies come from a few countries (eTable 1 in the Supplement). Herein, we use a study-replication design with data from 5 large and independent samples, addressing generalizability of results and the increasing concern of bias and nonreproducibility of results from research studies.[31,35]

Limitations

Our study has several limitations. Despite its large overall sample size, the effective sample size for individual countries was limited by the low prevalence of ASD. Misspecification is another potential limitation. The first potential misspecification arises from the possible violation of the assumption of independence between genetic and environment. If this correlation is not specifically included in the model, its components will mostly be incorporated into the estimate of genetic variance component, potentially biasing the heritability estimate. The direction of the bias will depend on the sign of the covariance between genetic and environmental factors.[36] The second misspecification arises from plausible gene-environment interactions that were not modeled and could also bias the heritability estimate. The direction of bias will depend on whether the environmental component is familial and whether the trait is multifactorial.[36] One potential interaction, or subgroup difference, is the difference in health care-seeking behavior between sister and sister and brother and brother. For example, sisters might be more likely to share information and encourage early identification in their children. To adjust for this, the model should allow for differences in shared environment effects for different parental sibling types or include an interaction between shared environment and sibling type, which would require an even larger sample size. Furthermore, misspecification of C and M will cause an upward bias of the M component because the M effect is the only effect that is sibling-type specific (correlation of M is only present in the sister-sister pair and absent in other sibling pairs). Nevertheless, because most of the M estimates are close to zero (Table 3), the risk of upward bias should be minimal. Any study using differences in ASD occurrence between sibling pairs will rely on the assumption of independent ascertainment. Lack of independence will make pairs more similar and may therefor inflate the contribution from the additive genetic effect as well as shared environment. Using differences in ASD variation between monozygotic and dizygotic twins could have strengthened the estimation of shared environment. However, because we did not have information about zygosity status and because twins are well known to have an el-

evated risk of being diagnosed with ASD[15] we excluded twins from our calculations.

Conclusions

Based on population data from 5 countries, in what is to our knowledge the largest study to date, the heritability of ASD was estimated to be approximately 80%, indicating that the variation in ASD occurrence in the population is mostly owing to inherited genetic influences, with no support for contribution from maternal effects. The results suggest possible modest differences in the sources of ASD risk between countries. The contributions of gene-environment interactions or correlations between genes and environment to ASD risk are important unanswered questions.

ARTICLE INFORMATION

Accepted for Publication: April 15, 2019.

Published Online: July 17, 2019. doi:10.1001/jamapsychiatry.2019.1411

Author Affiliations: Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR (Bai, Yip); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Yip, Mahjani, Hultman, Sandin); Center for Health Communities, Environmental Health Investigations Branch, California Department of Public Health, Richmond (Windham); Department of Child Psychiatry, Turku University, Turku University Hospital, Turku, Finland (Sourander, Suominen, Gissler); Telethon Kids Institute, Centre for Child Health Research, The University of Western Australia, Perth, Australia (Francis, Glasson, Leonard, Wong); Ministry of Health, Israel (Yoffe); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Mahjani, Buxbaum, Reichenberg, Sandin); Seaver Autism Center for Research and Treatment at Mount Sinai, New York, New York (Mahjani, Buxbaum, Reichenberg, Sandin); Information Services Department, National Institute for Health and Welfare, Helsinki, Finland (Gissler); Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden (Gissler); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Reichenberg); Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Reichenberg); Department of Public Health, Aarhus University, Aarhus, Denmark (Schendel); Department of Economics and Business, National Centre for Register-based Research, Aarhus University, Aarhus, Denmark (Schendel); iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus University, Aarhus, Denmark (Schendel); Department of Community Mental Health, University of Haifa, Haifa, Israel (Kodesh, Levine); Meuhedet Health Services, Israel (Kodesh); Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (Breshnahan); New York State Psychiatric Institute, New York (Breshnahan); Section for Biostatistics, Department of Public Health, Aarhus University, Aarhus, Denmark (Parner, Hansen).

Author Contributions: Drs Sandin and Reichenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bai, Yip, Sourander, Glasson, Buxbaum, Parner, Reichenberg, Sandin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bai, Sourander, Suominen, Kodesh, Levine, Reichenberg, Sandin.
Critical revision of the manuscript for important intellectual content: Bai, Yip, Windham, Sourander, Francis, Yoffe, Glasson, Mahjani, Leonard, Gissler, Buxbaum, Wong, Schendel, Breshnahan, Levine, Parner, Hansen, Hultman, Reichenberg, Sandin.
Statistical analysis: Bai, Yoffe, Mahjani, Suominen, Gissler, Levine, Parner, Reichenberg, Sandin.
Obtained funding: Sourander, Leonard, Buxbaum, Schendel, Breshnahan, Parner, Hultman, Reichenberg.
Administrative, technical, or material support: Bai, Sourander, Francis, Yoffe, Glasson, Gissler, Wong, Schendel, Kodesh, Breshnahan, Levine, Parner, Hultman, Reichenberg, Sandin.
Supervision: Yip, Buxbaum, Reichenberg, Sandin.

Conflict of Interest Disclosures: Dr Windham reported receiving grants from NIH sub-contract during the conduct of the study. Dr Sourander reported receiving grants from Academy of Finland Flagship Programme (decision No. 320162), Academy of Finland (decision No. 308552), the National Institutes of Health (NIH; W81XWH-17-1-0566), and the NIH (1U01HD073978-01) during the conduct of the study. Dr Francis reported receiving grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, and the National Institute of Neurological Disorders and Stroke during the conduct of the study. Ms Yoffe reported employment with the Israeli Ministry of Health, which did not fund the current research. Dr Leonard reported being a National Health and Medical Research Council Senior Research Fellow. Dr Buxbaum reported receiving grants from the Seaver Foundation during the conduct of the study. Dr Wong reported receiving grants from the NIH during the conduct of the study and grants from NHMRC outside the submitted work. Dr Breshnahan reported receiving grants from Columbia University during the conduct of the study. Dr Levine reported receiving research support from Shire Pharmaceuticals unrelated to the current research more than 3 years ago. Dr Sandin reported receiving grants from NIH during the conduct of the study. Dr Sandin reported being a Faculty Fellow of the Beatrice and Samuel A. Seaver Foundation. No other disclosures were reported.

Funding/Support: This study was supported by grant HD073978 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, and National Institute of Neurological Disorders and Stroke; and the Beatrice and Samuel A. Seaver Foundation (Dr Sandin is a Seaver Faculty Fellow). Dr Leonard is a National Health and Medical Research Council Senior Research Fellow. Data from Israel were ascertained through Israel Science Foundation grant 130/13.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The study data from Israel were obtained from the Ministry of the Interior and Ministry of Health and were analyzed in Israel, and the results may or may not reflect the views of these ministries.

REFERENCES

1. Lauritsen MB. Autism spectrum disorders. *Eur Child Adolesc Psychiatry*. 2013;22(suppl 1):S37-S42. doi:10.1007/s00787-012-0359-5

2. American Psychiatric Association. *Autism Spectrum Disorder*. 5th ed. Washington, DC: Diagnostic and Statistical Manual of Mental Disorders; 2013.

3. Kong A, Thorleifsson G, Frigge ML, et al. The nature of nurture: Effects of parental genotypes. *Science*. 2018;359(6374):424-428. doi:10.1126/science.aan6877

4. Yip BHK, Bai D, Mahjani B, et al. Heritable Variation, With Little or No Maternal Effect, Accounts for Recurrence Risk to Autism Spectrum Disorder in Sweden. *Biol Psychiatry*. 2018 83(7): 589-597. doi:10.1016/j.biopsych.2017.09.007

5. Svensson AC, Sandin S, Cnattingius S, et al. Maternal effects for preterm birth: a genetic epidemiologic study of 630,000 families. *Am J Epidemiol*. 2009;170(11):1365-1372. doi:10.1093/aje/kwp328

6. Devlin B, Daniels M, Roeder K. The heritability of IQ. *Nature*. 1997;388(6641):468-471. doi:10.1038/41319

7. Wang Y, Tang S, Xu S, Weng S, Liu Z. Maternal Body Mass Index and Risk of Autism Spectrum Disorders in Offspring: A Meta-analysis. *Sci Rep*. 2016;6:34248. doi:10.1038/srep34248

8. Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry*. 2016;57(5):585-595. doi:10.1111/jcpp.12499

9. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The heritability of autism spectrum disorder. *JAMA*. 2017;318(12):1182-1184. doi:10.1001/jama.2017.12141

10. Pettersson E, Lichtenstein P, Larsson H, et al; Attention Deficit/Hyperactivity Disorder Working

Group of the iPSYCH-Broad-PGC Consortium, Autism Spectrum Disorder Working Group of the iPSYCH-Broad-PGC Consortium, Bipolar Disorder Working Group of the PGC, Eating Disorder Working Group of the PGC, Major Depressive Disorder Working Group of the PGC, Obsessive Compulsive Disorders and Tourette Syndrome Working Group of the PGC, Schizophrenia CLOZUK, Substance Use Disorder Working Group of the PGC. Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychol Med*. 2019;49(7):1166-1173. doi:10.1017/S0033291718002039

11. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry*. 2011;68(11):1095-1102. doi:10.1001/archgenpsychiatry.2011.76

12. Le Couteur A, Bailey A, Goode S, et al. A broader phenotype of autism: the clinical spectrum in twins. *J Child Psychol Psychiatry*. 1996;37(7):785-801. doi:10.1111/j.1469-7610.1996.tb01475.x

13. Levine SZ, Levav I, Goldberg Y, Pugachova I, Becher Y, Yoffe R. Exposure to genocide and the risk of schizophrenia: a population-based study. *Psychol Med*. 2016;46(4):855-863. doi:10.1017/S0033291715002354

14. Schendel DE, Bresnahan M, Carter KW, et al. The International Collaboration for Autism Registry Epidemiology (iCARE): multinational registry-based investigations of autism risk factors and trends. *J Autism Dev Disord*. 2013;43(11):2650-2663. doi:10.1007/s10803-013-1815-x

15. Sandin S, Schendel D, Magnusson P, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry*. 2016;21(5):693-700. doi:10.1038/mp.2015.70

16. Langhoff-Roos J, Krebs L, Klungsøyr K, et al. The Nordic medical birth registers—a potential goldmine for clinical research. *Acta Obstet Gynecol Scand*. 2014;93(2):132-137. doi:10.1111/aogs.12302

17. McGuffin P, Owen MJ, Gottesman II. Quantitative genetics. In: McGuffin P, Owen MJ, Gottesman II, eds. *Psychiatric Genetics and Genomics*. Oxford, England: Oxford University Press; 2004: 44-48.

18. Lindström LS, Yip B, Lichtenstein P, Pawitan Y, Czene K. Etiology of familial aggregation in melanoma and squamous cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev*. 2007;16(8):1639-1643. doi:10.1158/1055-9965.EPI-07-0047

19. Yip BH, Moger TA, Pawitan Y. Genetic analysis of age-at-onset traits based on case-control family data. *Stat Med*. 2010;29(30):3258-3266. doi:10.1002/sim.3907

20. Pawitan Y, Reilly M, Nilsson E, Cnattingius S, Lichtenstein P. Estimation of genetic and environmental factors for binary traits using family data. *Stat Med*. 2004;23(3):449-465. doi:10.1002/sim.1603

21. Noh M, Yip B, Lee Y, Pawitan Y. Multicomponent variance estimation for binary traits in family-based studies. *Genet Epidemiol*. 2006;30(1):37-47. doi:10.1002/gepi.20099

22. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373(9659):234-239. doi:10.1016/S0140-6736(09)60072-6

23. Pawitan Y. *In All Likelihood: Statistical Modelling and Inference Using Likelihood*. Oxford, England: OUP Oxford; 2001.

24. Carter KW, Francis RW, Carter KW, et al; International Collaboration for Autism Registry Epidemiology. ViPAR: a software platform for the Virtual Pooling and Analysis of Research Data. *Int J Epidemiol*. 2016;45(2):408-416. doi:10.1093/ije/dyv193

25. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria; 2015.

26. Connolly N, Anixt J, Manning P, Ping-I Lin D, Marsolo KA, Bowers K. Maternal metabolic risk factors for autism spectrum disorder-An analysis of electronic medical records and linked birth data. *Autism Res*. 2016;9(8):829-837. doi:10.1002/aur.1586

27. Gardner RM, Lee BK, Magnusson C, et al. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study. *Int J Epidemiol*. 2015;44(3):870-883. doi:10.1093/ije/dyv081

28. Elks CE, den Hoed M, Zhao JH, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. *Front Endocrinol (Lausanne)*. 2012;3(29):29.

29. Chheda H, Palta P, Pirinen M, et al. Whole-genome view of the consequences of a population bottleneck using 2926 genome sequences from Finland and United Kingdom. *Eur J Hum Genet*. 2017;25(4):477-484. doi:10.1038/ejhg.2016.205

30. McEvoy BP, Montgomery GW, McRae AF, et al. Geographical structure and differential natural selection among North European populations. *Genome Res*. 2009;19(5):804-814. doi:10.1101/gr.083394.108

31. Ioannidis JPA. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124

32. Moonesinghe R, Khoury MJ, Janssens ACJW. Most published research findings are false-but a little replication goes a long way. *PLoS Med*. 2007;4(2):e28. doi:10.1371/journal.pmed.0040028

33. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. *JAMA*. 2014;311(17):1770-1777. doi:10.1001/jama.2014.4144

34. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. *Nat Genet*. 2014;46(8):881-885. doi:10.1038/ng.3039

35. Krishna Kumar S, Feldman MW, Rehkopf DH, Tuljapurkar S. Limitations of GCTA as a solution to the missing heritability problem. *Proc Natl Acad Sci U S A*. 2016;113(1):E61-E70. doi:10.1073/pnas.1520109113

36. Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. *Nat Rev Genet*. 2013;14(2):139-149. doi:10.1038/nrg3377