Can Sibling Sex Ratios Be Used as a Valid Test for the Prenatal Androgen Hypothesis of Autism Spectrum Disorders?

Permalink
https://escholarship.org/uc/item/5sf374fm

Journal
PloS one, 10(10)

ISSN
1932-6203

Authors
Cheslack-Postava, Keely
Susser, Ezra
Liu, Kayuet
et al.

Publication Date
2015

DOI
10.1371/journal.pone.0141338

Peer reviewed
Can Sibling Sex Ratios Be Used as a Valid Test for the Prenatal Androgen Hypothesis of Autism Spectrum Disorders?

Keely Cheslack-Postava¹, Ezra Susser²,3, Kayuet Liu⁴, Peter S. Bearman⁵*

¹ Department of Psychiatry, Columbia University, New York, New York, United States of America, ² Department of Epidemiology, Columbia University, New York, New York, United States of America, ³ New York State Psychiatric Institute, New York, New York, United States of America, ⁴ Department of Sociology, UCLA, Los Angeles, California, United States of America, ⁵ Interdisciplinary Center for Innovative Theory and Empirics, Columbia University, New York, New York, United States of America

* psb17@columbia.edu

Abstract

Background

Sibling sex ratios have been applied as an indirect test of a hypothesized association between prenatal testosterone levels and risk for autism, a developmental disorder disproportionately affecting males. Differences in sibling sex ratios between those with and without autism would provide evidence of a shared risk factor for autism and offspring sex.

Conclusions related to prenatal testosterone, however, require additional assumptions. Here, we used directed acyclic graphs (DAGs) to clarify the elements required for a valid test of the hypothesis that sibling sex ratios differ between children with and without autism.

Methods

Over 1.1 million subjects, born in California from 1992–2007, and identified through birth records, were included. The association between autism diagnosis, determined using the administrative database of the California Department of Developmental Services, and the sex of the subsequent sibling was examined using generalized estimating equations.

Results

Among male children with autism, 52.2% of next-born siblings were brothers, versus 51.0% for unaffected males. For females with autism, 50.2% of following siblings were brothers versus 51.2% among control females. The relative risk of a subsequent male sibling associated with autism diagnosis was 1.02 (95% confidence interval: 0.99, 1.04).
Conclusions

In a large, population-based sample we failed to find evidence suggesting an excess of brothers among children with autism while controlling for several threats to validity. This test cannot rule out a role of any given exposure, including prenatal testosterone, in either risk of autism or offspring sex ratio, but suggests against a common cause of both.

Introduction

Autism is a neurodevelopmental disorder involving impairments in social interaction, communication, and restricted or repetitive behaviours, noted for its marked but unexplained male preponderance. One well developed hypothesis proposed to explain this excess of male cases focuses on the idea of an ‘extreme male brain’—an exaggeration of typical sex differences shaped by prenatal factors, in particular, testosterone levels [1]. Under certain conditions discussed later, this hypothesis (henceforth termed the testosterone hypothesis) predicts that the sibling sex ratio will be different for children with autism compared with non-autistic children, that is, there will be an excess of male births among siblings of autistic children.

The current study had two goals. The first was to clarify the elements required to conduct a valid test of whether the sibling sex ratio differs for children with and without autism, consistent with the presence of a shared antecedent of both autism and sibling sex ratio. As detailed below, other causal structures may also give rise to an observed association between autism and sibling sex ratio. Our goal was to conduct a test such that an observed association would imply a shared antecedent factor. The second was to conduct such a test using a large, population-based sample of children with and without autism.

Some previous reports have indeed suggested an excess of male births among siblings of children with autism, and among siblings of children with related neurodevelopmental disorders [2–4]. Related disorders are relevant because male predominance is also evident in other disorders currently grouped as Autism Spectrum Disorder (ASD) in DSM-V, in disorders co-morbid with autism, and in many other neurodevelopmental disorders (i.e.[5–8]). These previous reports on sibling sex, however, had significant limitations. Generally they used relatively small and selected samples, and/or made comparisons with summary population values for the proportion of male births rather than with controls ascertained in a similar manner as cases, and/or did not meet some of the other criteria described below as conditions for a valid test. In the largest study thus far, significantly more males (58.5%) than expected (51.4%) were reported among 513 siblings of individuals with autism assessed at Danish clinics from 1960–1985 [3]. Siblings included were those reported at the time of clinical assessment, and expected sex ratio was based on the contemporary Danish live-birth ratios. Similar results were reported for developmental language disorder [4]. A much larger Danish register-based study was subsequently conducted, and did not find a significant difference in the sex ratio of siblings of people with ASD (50.8% male) relative to the live birth sex ratio from the corresponding years (51.3% male). Some differences for ASD subtypes were reported. Specifically, siblings of subjects with Asperger syndrome were less likely than expected to be male, whereas siblings of subjects with atypical autism were more likely to be male [9].

Conditions for a valid sibling sex ratio test

Legitimate questions could be raised about the explanatory power of the sibling sex ratio test for the testosterone hypothesis. For example, with longitudinal measurements of maternal and
foetal testosterone, one might construct a more direct test of the testosterone hypothesis. Although such designs have been explored, they have not yet been used in full studies, and are beyond the scope of this paper. Therefore we focus here only on conducting a valid sibling sex ratio test.

Three related premises are required for the use of the sibling sex ratio as a test of the testosterone hypothesis. The first premise is that children with autism and their siblings share a common cause that makes them more likely to be male than female. Thus, the predicted difference in sibling sex ratio of persons with versus without autism is due to confounding of the association between autism in one child and sex of their siblings rather than direct causation of sibling sex by autism. The second premise is that the common cause is prenatal testosterone. This premise is supported by some prior literature suggesting that higher prenatal testosterone levels could be shared by siblings and could increase the probability of offspring being male [10]. While the sex of a given individual is determined by an XX or XY chromosomal karyotype, the sex ratio of offspring at birth is dependent on both the ratio of male to female embryos at conception and their relative survival during gestation [11]. Previous applications of the sibling sex ratio test with regard to autism have focused on prenatal testosterone as an exposure hypothesized to influence this ratio. The observation of an association between autism and sibling sex ratio would also be compatible, however, with the presence of some other common cause. For example, maternal anxiety disorders [12] and exposure to stressful events [11] have been associated with variation in offspring sex ratios. The test presented here could equally be applied as evidence for or against their association with autism under corresponding assumptions. Our contribution here is to clarify the elements required for such a test and not to evaluate the evidence for or against any specific mechanisms hypothesized to affect sex ratios. The third premise is that autism in one child does not itself affect the probability that siblings are male versus female. A direct effect of autism on sibling sex would not represent a common cause shared by the siblings as postulated in the first premise. Although actually a corollary of the first premise, this third premise is worth noting explicitly because it is sometimes overlooked.

In order to explain the import of these premises for a valid test, we begin by portraying the different causal relationships that could underlie an observed association between autism and sibling sex ratio. We use directed acyclic graphs (DAGs), an increasingly common method for illustrating assumptions about causal associations between variables and determining how non-causal statistical associations may arise, explained in depth elsewhere [13;14]. In brief, a DAG is a diagram of assumed causal relationships in which variables are connected by arrows that point in one direction only; from cause to effect. In a DAG the absence of an arrow between two variables assumes that there is no direct causal effect between them. But there may still be a statistical association between the two variables, if they are connected by a series of arrows that form an “unblocked” pathway. An unblocked pathway is one that meets two conditions. First, it does not contain a “collider”, that is, a variable with two arrows pointing into it, i.e. a common effect of both variables. Second, given there is no collider, no variable in the path has been conditioned on (through adjustment, stratification, or restriction of the sample). Further properties of DAGs will be introduced when relevant in the scenarios below.

Five basic scenarios are depicted using DAGs in Fig 1. Each involves two characteristics, sex (S) and whether or not the person has an autism diagnosis (A), observed in each of two siblings (denoted by subscripts). Two siblings only are depicted for simplification but the concepts generalize to greater numbers of siblings. In each scenario, arrows from S_i to A_j indicate direct causal influence of “sex” on autism diagnosis, for example through a gender bias in case ascertainment [15], X-linked genes [16], or a “female protective effect” [17].

Fig.1A represents the “common cause” scenario that invokes the premises of the sibling sex ratio test described above. T represents prenatal levels of maternally produced testosterone.
A. Common cause

```
  T -----> S_1 -----> A_1 -----> A_2

             S_2
```

B. Sex independence

```
  G -----> S_1 -----> A_1 -----> A_2

             S_2
```

C. Sex independence

```
  S_1 -----> A_1 -----> A_2

             S_2
```

D. Separate causes

```
  T -----> S_1 -----> A_1 -----> A_2

             S_2

  G -----> A_1 -----> A_2
```

E. Autism independence

```
  T -----> S_1 -----> A_1 -----> A_2

             S_2
```
Individual levels of serum testosterone are correlated over time in women of reproductive age [18]. Arrows from T to S and A in each child depict the joint hypothesis that maternal prenatal testosterone levels affect both sex and risk of autism in each child.

Fig 1B shows one kind of “sex independence” scenario. A factor G is associated with risk of autism in each child, but that factor is unrelated to observed sex. G for example could be parental genotypes or a stable perinatal or environmental factor. In the scenario depicted, there is no association between A1 and S2 in a population, because the path between them is blocked at the collider A2. An artifactual association could be created, however, by study designs that are often employed. In a study design where a study subject from each family is selected based on having autism (i.e., all A1 have autism), it will then follow that the siblings of these study subjects (i.e. A2) are selected as less likely than by chance to have autism. This is despite the sibling recurrence risk of autism, and will occur because persons in the population with autism have been disproportionately designated as “subjects” rather than “siblings”. This is referred to as “conditioning on a collider” and unblocks the path through A2, creating an unblocked path from A1 to G to A2 to S2 in Fig 1B. A statistical association between autism and sibling sex ratio may be observed as a result of opening this path, but such an association will be artifactual, that is, attributable to selection bias in the study design [19].

Fig 1C shows another “sex independence” scenario. An example of this scenario would be when observed autism in one child affects observed autism in the second child directly (arrow from A1 to A2) through dynamics of ascertainment. The potential to observe association between A1 and S2 could arise similarly as in scenario 1B, described above.

Fig 1D shows a “separate causes” scenario. Separate factors influence sex and autism risk in all children. This diagram would apply for example if it was in fact the case that maternal testosterone influences probability of producing a male or female zygote (S), but does not affect autism risk; however other factors shared between siblings (G) do influence autism risk.

Yet another potential scenario of “autism independence” is depicted in Fig 1E. In this scenario, there is a shared cause for S in each child, but not for A. In scenarios 1D and 1E, an association between A1 and S2 would be observed due to the unblocked path from A1, to S1, to the shared cause, T, of sex in both children, to S2.

The proposed idea behind examining sibling sex ratios in cases with autism is to infer the type of association shown in Fig 1A. Therefore, a sibling sex ratio test should show an association between autism in the individual selected as the “subject” and sex of subject siblings under the scenario depicted in Fig 1A, but not those shown in Fig 1B, 1C, 1D and 1E. Two additional situations may pose threats to the validity of the test by inducing an observed association under scenarios other than 1A. First, the presence of any time stable factor other than testosterone which is causally associated with both sex and autism diagnosis will introduce confounding. Second, as illustrated in Fig 2, a type of selection bias could occur if the decision to have additional children is influenced by both the sex composition of prior children (i.e. to fulfill a preference for children of each sex) and by autism diagnosis in prior children (i.e. parents...
of healthy children may be more likely to have additional children than are parents of children with an illness or disability). Needless to say, only children who are actually born can be observed and included in a study. Therefore, if the sex composition and autism diagnosis of children within a family jointly affect whether or not additional siblings are born into that family (denoted by \( O \) in Fig 2), then autism in one child, \( A_n \), and sex of the next child, \( S_{n+1} \), will become associated, following the unblocked path from \( A_n \) through the collider, \( O_{n+1} \), to \( S_n \) to \( T \), to \( S_{n+1} \) (Fig 2).

Conditions to ensure that an association between autism in the individual selected as the “subject” and sex of subject siblings will be observed if the “true” underlying scenario is that depicted in Fig 1A, but not if it is one of those shown in Fig 1B, 1C, 1D and 1E; or in Fig 2A and 2B (which are extensions of scenarios 1D and 1E), are summarized in Table 1.

**Methods**

**Data Structure**

Sibships were identified from data on all births in the state of California from the years 1985–2007, obtained from state Birth Master Files (California Department of Public Health, [www.cdph.ca.gov](http://www.cdph.ca.gov)). Infants known to have died before age 1 were excluded. Full siblings were

---

**Fig 2. Possible causal structures underlying a selection bias induced association between autism and sibling sex.** Preferences regarding sex composition may affect future fertility decisions, and hence observation (O) of additional siblings. This is represented here by arrows from sexes of child 1 and 2, \( S_1 \) and \( S_2 \), to \( O_3 \), the observation (or not) of a third child. If either autism in previous children (\( A_1 \) and \( A_2 \)), or shared factors associated with autism (U; e.g., parental age at the start of childbearing) also affect future fertility, selection bias may result. This is due to de facto conditioning on \( O_3 \) (only children who are conceived and born may be observed), opening a blocked path between autism and child sex. Conditioning on the sex of prior children will block these paths. A box drawn around a variable represents conditioning on it, which, unless it is a collider, blocks any paths through it.

doi:10.1371/journal.pone.0141338.g002
identified by matching on: child’s last name; mother’s first name, maiden name, birth place, race, and Hispanic ethnicity; and father’s race and Hispanic ethnicity. Scrambled versions of all names were used to protect privacy. Consistency of the matches was checked against mother’s birth year and father’s birth year derived from mother’s age and father’s age on the birth record.

**Study subjects**

The selection of study subjects is outlined in **Table 2**. Children born from 1992–2007 comprised the total pool of potential study subjects. Children were excluded if they were not linked to one or more siblings. Families including twins or higher multiple births were excluded. Additionally, children were excluded due to possible erroneous sibling matches if the birth certificate maternal date of last live birth was discordant with prior linked sibling’s date of birth or if any members of the linked sibship included mismatched sequences based on maternal number of live births from birth certificates versus children’s birth dates. Finally, children were excluded if one or more preceding sibling (based on reported number of prior maternal live births) was missing from the data structure, which would preclude control for existing sex composition of the family. Among the children who remained eligible to be study subjects after these exclusions, we selected as our study subjects the 1,192,219 children who had a subsequent sibling observed in the data set (i.e. data on “outcome” was available, see below) and who had data available on all covariates. Although children born from 1985–1991 were not eligible to be subjects because information on autism diagnosis (“exposure”, see below) was only available beginning in 1992, they could still contribute information about family composition.

### Table 1. Summary of criteria for a valid sibling sex ratio test.

| Criterion and justification | Scenario(s) which criterion is required to rule out |
|-----------------------------|---------------------------------|
| **Condition on sex of the subject** |
| Controlling for subject sex (S1) blocks the only open path between A1 and S2 in Fig 1D and 1E, whereas in Fig 1A they remain associated. | D, E |
| **Do not condition or select on autism in subjects** |
| Induces association by opening path blocked by a collider at A2. Preferentially selecting a subject with autism from all affected families will have this effect by making siblings less likely than random to have autism. | B, C |
| **Control for sex composition of previous children** |
| Preferences regarding sex composition may affect future fertility decisions, and hence observation of additional siblings. If either autism in previous children, or factors associated with autism (ex. parental age) also affect future fertility, selection bias may result (Fig 2). Controlling for the sex of the subject and preceding children blocks the open paths through which this biased association would flow. | D, E |
| **Consider sex of next sibling only** |
| Follows from previous item; otherwise sex composition of previous children will be incompletely controlled. | D, E |
| **Control for potential confounders** |
| Required to attribute an observed association to prenatal testosterone (or any other specifically hypothesized factor; versus alternative confounding factor). | B, C, D, E |

doi:10.1371/journal.pone.0141338.t001
Exposure
The independent variable ("exposure") for analyses was presence/absence of an autism diagnosis in a study subject. Children diagnosed with autism were identified using client records of California’s Department of Developmental Services (DDS; www.dds.ca.gov) from July 1, 1992 through June 30, 2011. DDS provides services to persons with autism and other developmental disabilities such as mental retardation, epilepsy, and cerebral palsy; other autism spectrum disorders including Asperger syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS) alone do not qualify a person for services. It has previously been estimated that the DDS system includes 75–80% of children with autism in the state [20].

Outcome
The dependent variable ("outcome") was sex of a subject’s next sibling. Sex of children at birth was determined from the birth master file. Information on sibling sequence was derived within matched sibling sets from birth dates and maternal reported total number of previous live births for each child.

Statistical Analyses
In order to determine the association between autism diagnosis and sex of the next sibling, while accounting for potential correlation between subjects from the same family, we fit a series of log binomial models using generalized estimating equations with an exchangeable correlation structure and robust variance estimates. In each of these models, autism in the subject was the independent variable, and sex of the next sibling was the dependent variable. In addition to an unadjusted model, models were fit to address concerns enumerated in Table 1. These included models: a) adjusted for subject sex; b) adjusted for potential confounders (maternal and paternal age; maternal race, education, birthplace, parity and payment for delivery using Medi-Cal); c) adjusted for number and sex composition of children to date (categorized as all male, all female, or both); and d) including a product term between subject autism and subject sex, in order to derive separate estimates for male and female subjects. Difference in the male and female estimates was assessed using the product term p-value. All analyses were conducted using Stata version 11.2 (StataCorp LP, College Station, TX). Approval for this study was given by the institutional review board of Columbia University with a waiver of informed consent. Subject information was anonymized prior to analysis.
Results

The percentage of the population that was male in each step of subject selection is given in Table 2. 51.1% of births in the underlying cohort were male, and this proportion held among those births that matched to one or more siblings. The births that met eligibility criteria for inclusion with regard to data quality and completeness for sibling sequence within families, and had complete covariate data, were 51.4% male. Finally, the subset of those births where a next sibling (“outcome”) was observed were 51.6% male.

Results for analyses showing the association of autism with sex of next siblings are presented in Table 3. 51.9% of study subjects with autism and 51.1% of study subjects without autism had a brother as the next sibling (unadjusted RR [95% CI] = 1.02 [0.99, 1.04]. This estimate of association was essentially unchanged after adjustment for subject sex (RR = 1.02), potential confounders (RR = 1.02), or the number and sex composition of previous children (RR = 1.02).

For male and female study subjects considered separately, results for unadjusted analysis were RR (95% CI) = 1.02 [1.00, 1.05]; p > 0.05 and RR = 0.98 [0.92, 1.04] respectively. The model including a product term between subject’s sex and autism diagnosis (p = 0.19) did not provide evidence that male and female subjects varied in their associations between autism diagnosis and sex of the subsequent sibling.

Discussion

The report here is to our knowledge the most rigorous exploration to date of whether autism in a child is associated with male sex in his/her siblings. Sibling sex ratios have been proposed as a test of hypotheses about the role of prenatal testosterone in influencing the development of autism, and we challenge here how they can be validly used for this purpose. We compared 6,690 children who had autism with controls drawn from the same population, and found no evidence that the two groups differed with respect to the next sibling being male (adjusted RR = 1.02, p > 0.05).

Our results are concordant with those of the only prior large-scale study to examine sibling sex-ratios in autism [9], but in contrast to previous reports of such an association, for autism

Table 3. Relative risks that next sibling is male among subjects with versus without Department of Developmental Services (DDS) autism diagnoses among California births, 1992–2003.

|                | N cases | % male (sex ratio), next sibling of ASD cases | % male (sex ratio), next sibling of non-cases | RR [95% CI] | p int |
|----------------|---------|---------------------------------------------|---------------------------------------------|-------------|-------|
| Unadjusted     | 6690    | 51.9 (1.08)                                 | 51.1 (1.04)                                 | 1.02 [0.99, 1.04] |       |
| Adjusted for sex of subject |         |                                             |                                             | 1.02 [0.99, 1.04] |       |
| Adjusted for potential confounders<sup>a</sup> |         |                                             |                                             | 1.02 [0.99, 1.04] |       |
| Adjusted for potential selection factors<sup>b</sup> |         |                                             |                                             | 1.02 [0.99, 1.04] |       |
| Male subject   | 5598    | 52.2 (1.09)                                 | 51.0 (1.04)                                 | 1.02 [1.00, 1.05]<sup>c</sup> | 0.19 |
| Female subject | 1092    | 50.2 (1.01)                                 | 51.2 (1.05)                                 | 0.98 [0.92, 1.04] |       |

<sup>a</sup> Paternal age; and maternal age, race, education, birthplace, Medi-Cal, and parity.

<sup>b</sup> Number and sex composition (girls only, boys only, both) of previous-born, living children.

<sup>c</sup> p > 0.05.

doi:10.1371/journal.pone.0141338.t003
or for ‘male-biased’ disorders including autism [2]. Possible explanations for these differences in prior studies include chance findings in smaller samples; selected samples; and comparison to sex ratios derived from overall populations rather than comparably selected controls (see [21] for an example where this makes a substantive difference).

The sibling sex ratio test conducted here is not a direct test of the hypothesis that maternal testosterone affects autism. Rather, it is a test for evidence of a shared factor influencing both autism and offspring sex ratio. As such, the sibling sex ratio test conducted here does not support the hypothesis that any shared factor (including maternal testosterone) affects both autism and sex of offspring. Three alternative hypotheses would be consistent with the observations made here: 1) maternal testosterone influences autism but not sex in offspring; 2) maternal testosterone influences sex but not autism in offspring; 3) maternal testosterone influences neither sex nor autism in the offspring. We note that this reasoning would equally apply to any other hypothesized shared cause of autism and offspring sex ratio. With regard to the testosterone hypothesis, a fourth explanation, instability of maternal testosterone levels over time, would allow for causal effects of maternal testosterone on both child sex and risk of autism, but posit sufficient variation in within-woman levels over time so that exposure levels and associated outcomes between offspring are uncorrelated. Longitudinal evidence [18] as well as a role of genetic factors in determining levels [22;23] suggests a stable component, but data here cannot eliminate this explanation. However, it should be noted that this would negate the hypothetical utility of a sibling sex ratio test. Similar consideration of temporal variability should be given to any other hypothesized shared exposure for which this test would be applied.

Limitations should be noted. The study used administrative data, and neither diagnosis nor parentage was verified using clinical or laboratory methods; however, several exclusion criteria were applied to reduce the probability of including incorrectly matched siblings. Meanwhile, sex of children is unlikely to be misclassified. This study pertains to children with a diagnosis of autism, and may not reflect other ASD classifications which are not eligible for services through DDS. As with any study, there exists the potential for confounding by unmeasured factors. In order to diminish a true association between autism and subsequent male siblings, a factor would have to be such that levels associated with higher risk of autism diagnosis were associated with lower probability of subsequent male births. We cannot rule this out but note that adjustment for recognized potential confounders made virtually no difference in estimates of association.

The findings presented here call attention to several key issues in interpreting results from epidemiologic studies with regard to sibling sex ratios. First, relatively small studies, such as those that have previously been cited as confirmatory evidence for this explanation of autism and other disorders [24–27], are prone to statistical imprecision. The findings that make it into the literature are most likely to be those that both reach or approach statistical significance (as defined by p-values <0.05), and by extension, those that overestimate the magnitude of any true association. Second, very large studies, including the one reported here, are prone to findings of statistically significant so-called “tiny effects” [28] which are difficult to interpret both with regard to clinical or etiologic relevance and given the omnipresent possibility of residual bias. Even so, the very low magnitude of association between autism and sibling sex reported here failed to reach the traditional benchmark of “statistical significance”. Finally, no matter what the study size, sources of potential bias should be recognized. Adequately addressing such potential bias requires using a control population ascertained in a comparable manner to cases, and cannot be accomplished through a simple comparison to overall population statistics [24–28]. We suggest that future studies examining sibling sex ratios in autism spectrum disorders, or any outcome, should use large, population-based sources of data and rigorous methods to minimize bias.
In conclusion, our results from a large California population do not provide evidence that the sex of a child’s next sibling is associated with whether or not that child has an autism diagnosis, and do not support the joint hypothesis that any common factor (including prenatal testosterone levels) is causally related to both sex and risk of autism among offspring.

Author Contributions
Conceived and designed the experiments: KCP ES KL PB. Performed the experiments: KCP KL. Analyzed the data: KCP KL. Wrote the paper: KCP ES KL PB.

References
1. Knickmeyer RC, Baron-Cohen S. Fetal testosterone and sex differences in typical social development and in autism. J Child Neurol. 2006 Oct; 21(10):825–45. PMID: 17005117
2. James WH. Further evidence that some male-based neurodevelopmental disorders are associated with high intrauterine testosterone concentrations. Med Dev Child Neurol. 2008 Jan; 50(1):15–8. doi: 10.1111/j.1469-8749.2007.02001.x PMID: 18173623
3. Mouridsen SE, Rich B, Isager T. Sibling sex ratio of individuals diagnosed with autism spectrum disorder as children. Dev Med Child Neurol. 2010 Mar; 52(3):289–92. doi: 10.1111/j.1469-8749.2009.03368.x PMID: 19549197
4. Mouridsen SE, Hauschild KM. The sex ratio of siblings of individuals with a history of developmental language disorder. Logoped Phoniatr Vocol. 2010 Oct; 35(3):144–8. doi: 10.3109/140154030518007 PMID: 20735173
5. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009 Jun; 65(6):591–8. doi: 10.1203/PDR.0b013e3181e7203 PMID: 19218885
6. Lai DC, Tseng YC, Hou YM, Guo HR. Gender and geographic differences in the prevalence of intellectual disability in children: analysis of data from the national disability registry of Taiwan. Res Dev Disabil. 2012 Nov; 33(6):2301–7. doi: 10.1016/j.ridd.2012.07.001 PMID: 22877930
7. Rutter M, Caspi A, Fergusson D, Horwood LJ, Goodman R, Maughan B, et al. Sex differences in developmental reading disability: new findings from 4 epidemiological studies. JAMA 2004 Apr 28; 291 (16):2007–12. PMID: 15113820
8. Suren P, Bakken IJ, Aase H, Chin R, Gunnes N, Lie KK, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics 2012 Jul; 130(1):e152–e158. doi: 10.1542/peds.2011-3217 PMID: 22711729
9. Mouridsen SE, Rich B, Isager T. The sex ratio of full and half siblings of people diagnosed with an autism spectrum disorder: a Danish Nationwide Register Study. Child Psychiatry Hum Dev. 2014 Oct; 45(5):493–9. doi: 10.1007/s10578-013-0419-1 PMID: 24213328
10. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. J Endocrinol. 2008 Jul; 198(1):3–15. doi: 10.1677/JOE-07-0446 PMID: 18577567
11. Catalano R, Yorifuji T, Kawachi I. Natural selection in utero: evidence from the Great East Japan Earthquake. Am J Hum Biol. 2013 Jul-Aug; 25(4):555–9. doi: 10.1002/ajhb.22414 PMID: 23754635
12. Subbaraman MS, Goldman-Mellor SJ, Anderson ES, Lewinn KZ, Saxton KB, Shumway M, et al. An exploration of secondary sex ratios among women diagnosed with anxiety disorders. Hum Reprod. 2010 Aug; 25(8):2084–91. doi: 10.1093/humrep/deq166 PMID: 20570972
13. Glymour MM, Greenland S. Causal Diagrams. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. Third ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 183–212.
14. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999 Jan; 10(1):37–48. PMID: 9888279
15. Cheslack-Postava K, Jordan-Young RM. Autism spectrum disorders: Toward a gendered embodiment model. Soc Sci Med. 2012 Jun; 74(11):1667–74. doi: 10.1016/j.socscimed.2011.06.013 PMID: 21803468
16. Marco EJ, Skuse DH. Autism-lessons from the X chromosome. Soc Cogn Affect Neurosci. 2006 Dec; 1 (3):183–93. doi: 10.1093/scan/nsl028 PMID: 16985105
17. Robinson EB, Lichtenstein P, Anckarsater H, Happe F, Ronald A. Examining and interpreting the female protective effect against autistic behavior. Proc Natl Acad Sci U S A 2013 Mar 26; 110 (13):5258–62. doi: 10.1073/pnas.1211070110 PMID: 23431162
18. Apter D, Vihko R. Endocrine determinants of fertility: serum androgen concentrations during follow-up of adolescents into the third decade of life. J Clin Endocrinol Metab. 1990 Oct; 71(4):970–4. PMID: 2144859
19. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004 Sep; 15(5):615–25. PMID: 15308962
20. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord. 2002 Jun; 32(3):207–15. PMID: 12108622
21. Flannery KA, Liederman J. A re-examination of the sex ratios of families with a neurodevelopmentally disordered child. J Child Psychol Psychiatry 1996 Jul; 37(3):621–3. PMID: 8807444
22. Harris JA, Vernon PA, Boomsma DI. The heritability of testosterone: a study of Dutch adolescent twins and their parents. Behav Genet. 1998 May; 28(3):165–71. PMID: 9670592
23. Hoekstra RA, Bartels M, Boomsma DI. Heritability of testosterone levels in 12-year-old twins and its relation to pubertal development. Twin Res Hum Genet. 2006 Aug; 9(4):558–65. PMID: 16899163
24. James WH. Hypothesis: one cause of polydactyly. J Theor Biol. 1998 May 7; 192(1):1–2. PMID: 9628834
25. James WH. Is transposition of the great arteries a consequence of maternal hormone imbalance? Evidence from the sex ratios of relatives of probands. J Theor Biol. 1999 Jun 7; 198(3):301–3. PMID: 10366488
26. James WH. Are oral clefts a consequence of maternal hormone imbalance? evidence from the sex ratios of sibs of probands. Teratology 2000 Nov; 62(5):342–5. PMID: 11029152
27. James WH. Evidence that intrauterine and postnatal androgens affect the development of pyloric stenosis. Birth Defects Res A Clin Mol Teratol. 2004 Jan; 70(1):37–9. PMID: 14745993
28. Siontis GC, Ioannidis JP. Risk factors and interventions with statistically significant tiny effects. Int J Epidemiol. 2011 Oct; 40(5):1292–307. doi: 10.1093/ije/dyr099 PMID: 21737403