

# DOCUMENT SUMMARY

This 2022 research article provides strong empirical evidence for the "female protective effect" (FPE) in autism, the theory that females require a greater genetic and etiological load to receive an autism diagnosis. By comparing autistic males with an autistic sister to those with only autistic brothers, the study found that males from female-containing families exhibit more severe impairments in motor skills and adaptive functioning. Crucially, no difference was found in core social communication symptoms. This paper is core to Enlitens' mission as it scientifically validates the existence of a diagnostic bias against females, explains why their presentation may differ (potentially with fewer non-social impairments), and powerfully supports the need for more nuanced, individualized assessment methods beyond standardized tools calibrated to a male phenotype.

## FILENAME

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## METADATA

- **Primary Category:** NEURODIVERSITY
- **Document Type:** research\_article
- **Relevance:** Core
- **Key Topics:** female protective effect (FPE), autism, sex differences, diagnostic bias, genetics, motor skills, adaptive functioning, women
- **Tags:** #female\_protective\_effect, #FPE, #autism, #sex\_differences, #diagnostic\_bias, #genetics, #women, #motor\_skills, #adaptive\_skills, #liability\_threshold\_model, #vineland, #SRS

## CRITICAL QUOTES FOR ENLITENS

"The reduced prevalence of autism in females has been hypothesized to be a result of a female protective effect (FPE), wherein females require a greater etiological load—genetic and/or environmental—to be diagnosed with autism when compared to males."

"According to this model, if an autistic female is diagnosed, her family is likely to carry a greater etiological load for autism than families with only autistic males. Therefore, the FPE predicts that the autistic siblings of autistic females should, on average, present with more severe autistic traits."

"Here, we tested this central hypothesis of the FPE by comparing the severity of autistic traits in a large, well-characterized cohort of 609 autistic males with at least one autistic sister (from

'female-containing' multiplex families) and 2038 autistic males with only autistic brothers (from 'male-only' multiplex families)."

"Consistent with the FPE, we found that autistic males with an autistic sister demonstrated significantly more severe restricted and repetitive behaviors, and greater motor and adaptive skills deficits than autistic males with only autistic brothers."

"Notably, we did not find a significant difference in social communication deficits between the two groups of autistic males. Our findings suggest that the FPE may not uniformly impact all autistic traits, but rather may have a greater effect on non-social traits such as motor skills and adaptive behaviors."

"Our study provides strong evidence for the FPE in autism and suggests that the FPE has a greater impact on non-social autistic traits. These findings have important implications for both the diagnosis and underlying neurobiology of autism in females."

## KEY STATISTICS & EVIDENCE

- **Study Population:** The study analyzed data from two large repositories: the Simons Simplex Collection (SSC) and the Simons Powering Autism Research for Knowledge (SPARK) database.
- **Sample Size:** The final sample consisted of 2,647 autistic males from multiplex families (families with more than one autistic child).
  - 609 autistic males were from "female-containing" (FC) multiplex families (i.e., had at least one autistic sister).
  - 2,038 autistic males were from "male-only" (MO) multiplex families (i.e., had only autistic brothers).
- **Primary Finding:** Autistic males from FC families had significantly more severe impairments in non-social domains compared to autistic males from MO families.
  - **Motor Skills:** On the Vineland Adaptive Behavior Scales (VABS-II), males from FC families had significantly lower (more impaired) scores in Motor Skills ( $p = 0.005$ ).
  - **Adaptive Behavior:** Males from FC families also had significantly lower scores on the VABS-II Adaptive Behavior Composite ( $p = 0.045$ ).
- **No Difference in Social Communication:** There was **no significant difference** between the two groups of males on measures of social communication deficits, including the Social Responsiveness Scale (SRS-2) Total Score ( $p = 0.17$ ) and the ADOS-2 Social Affect score ( $p = 0.53$ ).
- **Restricted and Repetitive Behaviors (RRBs):** Autistic males from FC families showed significantly more severe RRBs as measured by the ADOS-2 Restricted and Repetitive Behavior score ( $p = 0.038$ ).

## THEORETICAL FRAMEWORKS

### The Female Protective Effect (FPE)

The central framework of the paper, which posits that biological females are inherently more resistant to the etiological factors that cause autism.

- **Definition:** "The reduced prevalence of autism in females has been hypothesized to be a result of a female protective effect (FPE), wherein females require a greater etiological load—genetic and/or environmental—to be diagnosed with autism when compared to males".
- **Mechanism:** The biological mechanisms are unknown but are theorized to be a combination of genetic, hormonal, and immunological factors that buffer females against developing an autistic phenotype at a lower etiological load.

## Liability-Threshold Model

This is the statistical and conceptual model that underlies the FPE.

- **Concept:** It assumes that there is an underlying, continuous "liability" for autism in the population, which is composed of all relevant genetic and environmental risk factors. An individual is diagnosed with autism only when their liability crosses a certain diagnostic "threshold".
- **FPE within the Model:** The FPE proposes that the diagnostic threshold is **higher for females** than for males. Consequently, a female must accumulate a greater liability (more risk factors) to cross this higher threshold and be diagnosed.
- **Prediction for Families:** "A key prediction of this model is that if a female is diagnosed with autism, her family must carry a greater liability for autism than families with only male autistics. It therefore follows that the autistic siblings of autistic females should present with more severe autistic traits than the autistic siblings of autistic males". This study was designed to directly test this prediction.

# METHODOLOGY DESCRIPTIONS

## Participant Selection

Participants were drawn from the Simons Simplex Collection (SSC) and SPARK databases. The study focused on autistic males from two types of multiplex families:

- **Female-Containing (FC) Multiplex Families:** Families with at least one diagnosed autistic daughter and at least one diagnosed autistic son. The autistic sons from these families formed the FC male group.
- **Male-Only (MO) Multiplex Families:** Families with at least two diagnosed autistic sons and no diagnosed autistic daughters. The autistic sons from these families formed the MO male group.

## Measures Used

A range of standardized instruments were used to quantify autistic traits, cognitive ability, and adaptive functioning.

- **Autism Diagnostic Observation Schedule, Second Edition (ADOS-2):** A semi-structured, standardized assessment of social affect (SA), restricted and repetitive behaviors (RRB), and other behaviors associated with autism. The Calibrated Severity Score (CSS) was used for comparison.
- **Social Responsiveness Scale, Second Edition (SRS-2):** A quantitative measure of autistic social impairment, completed by a parent/caregiver.
- **Repetitive Behavior Scale-Revised (RBS-R):** A parent-report questionnaire measuring the presence and severity of repetitive behaviors.
- **Vineland Adaptive Behavior Scales, Second Edition (VABS-II):** A parent-report measure assessing adaptive functioning in three domains: Communication, Daily Living Skills, and Socialization. It also provides an Adaptive Behavior Composite score. An optional Motor Skills domain is included for younger children.
- **Full-Scale Intelligence Quotient (FSIQ):** Assessed using various standardized IQ tests appropriate for the participant's age and verbal ability (e.g., Wechsler scales, Differential Ability Scales-II, Mullen Scales of Early Learning).

## PRACTICAL APPLICATIONS

### Implications for Diagnosis of Females

The study's findings have significant implications for clinical practice and the diagnosis of autism in females.

- **Diagnostic Bias:** The results provide strong evidence for a diagnostic bias. Since females require a greater etiological load to be diagnosed, the current diagnostic criteria, heavily based on male presentations, are likely missing females who have a lower load but still meet the threshold for being autistic.
- **Rethinking Core Symptoms:** The finding that the FPE has a greater impact on non-social domains (motor skills, adaptive functioning) than on social communication is crucial. "Our findings suggest that autistic females who receive a diagnosis may present with more severe non-social deficits, and that females with less severe non-social deficits may be missed by current diagnostic practices". This challenges the simplistic notion that females are missed only because they are "better at masking" social difficulties. It suggests clinicians should be aware that an autistic girl or woman may present with significant social challenges but relatively intact motor and adaptive skills, and this presentation should not rule out a diagnosis.
- **Need for New Assessment Tools:** The study highlights the inadequacy of current assessment tools that may not be sensitive to the female phenotype of autism. This reinforces the need for more nuanced, qualitative, and individualized assessment methods, like the Enliten Interview, that can look beyond a checklist of behaviors calibrated on male-only or male-majority samples.