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# Sex differences in Tourette syndrome and related disorders

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# Tourette's Syndrome: What Are the Influences of Gender and Comorbid Obsessive-Compulsive Disorder?

SUSAN L. SANTANGELO, Sc.D., DAVID L. PAULS, Ph.D., JILL M. GOLDSTEIN, Ph.D.,  
STEPHEN V. FARAONE, Ph.D., MING T. TSUANG, M.D., Ph.D., D.Sc., AND JAMES F. LECKMAN, M.D.

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 33:6, JULY/AUGUST 1994

- n=92 (74% males), 32 were adults (56% men).
- Females: older than males at diagnosis (**21 +/- 14y** vs **14 +/- 10y**); no difference in age at onset.

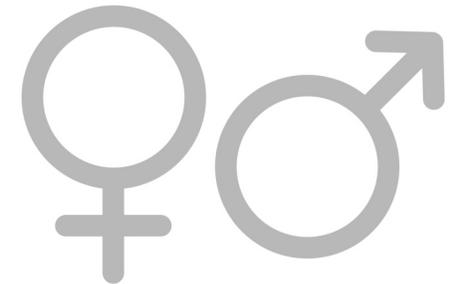
	Tics Experienced at Onset		Tics Experienced Ever	
	M (%)	F (%)	M (%)	F (%)
Simple motor	54	63	71	54
Simple vocal	29	38	88	67 <sup>e</sup>
Any simple	65	71	96	80 <sup>f</sup>
Complex motor	28	46	100	100
Complex vocal	6	4	90	96
Any complex	32	46	100	100
Compulsive	19	38	97	96





## TOURETTE SYNDROME: a male bias

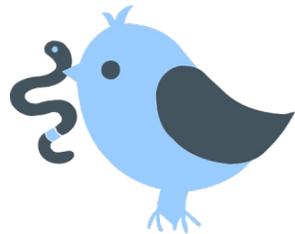
- **Like in other neurodevelopmental disorders** (ASD, ADHD), there is a male predominance in Tourette syndrome (TS).
- **Attenuation with age:**
  - Childhood: Sex ratio 3-4 M : 1F.<sup>1</sup>
  - Adulthood: Sex ratio 2 M : 1F.<sup>2,3</sup>



***Are there sex-specific phenotypes and prognoses for TS?***

<sup>1</sup>Knight et al, 2012; <sup>2</sup>Schlender et al., 2011; <sup>3</sup>Yang et al., 2016.

# OVERVIEW OF THE TALK



1. Sex differences in tic disorders in childhood
2. Sex differences in tic disorders in adults & our experience from The Calgary and Paris Adult Tic Registry
3. Substrates of sex differences in tic disorders
4. Evidence from other disorders
5. Take home messages

# Exploration of sex differences in tic disorders in childhood



# HIGHER TIC SEVERITY IN YOUNG FEMALES

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY

ORIGINAL ARTICLE



## Influence of sex on tic severity and psychiatric comorbidity profile in patients with pediatric tic disorder

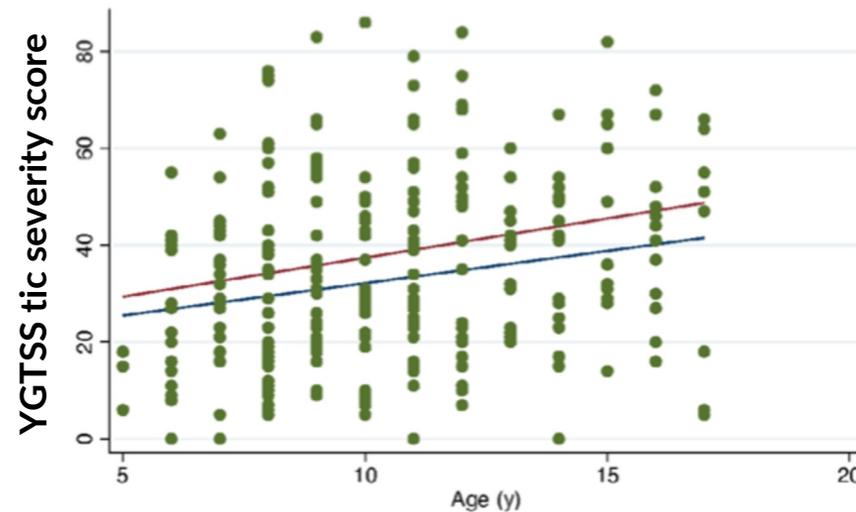
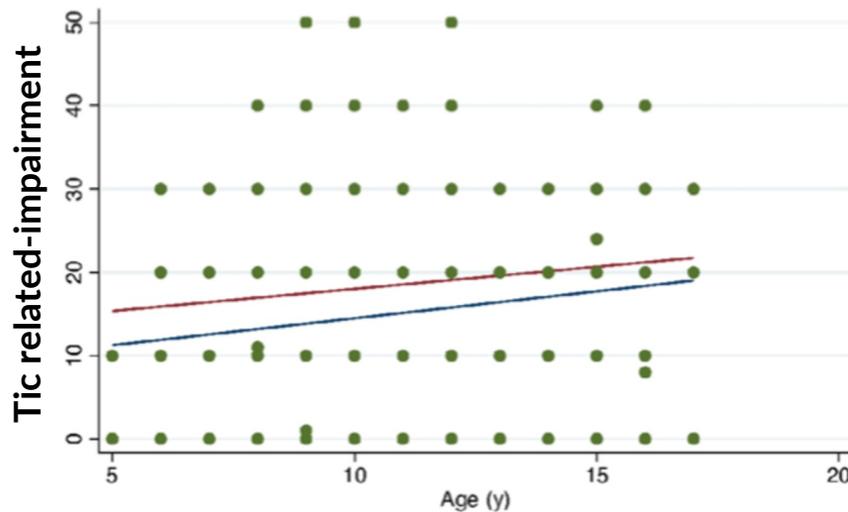
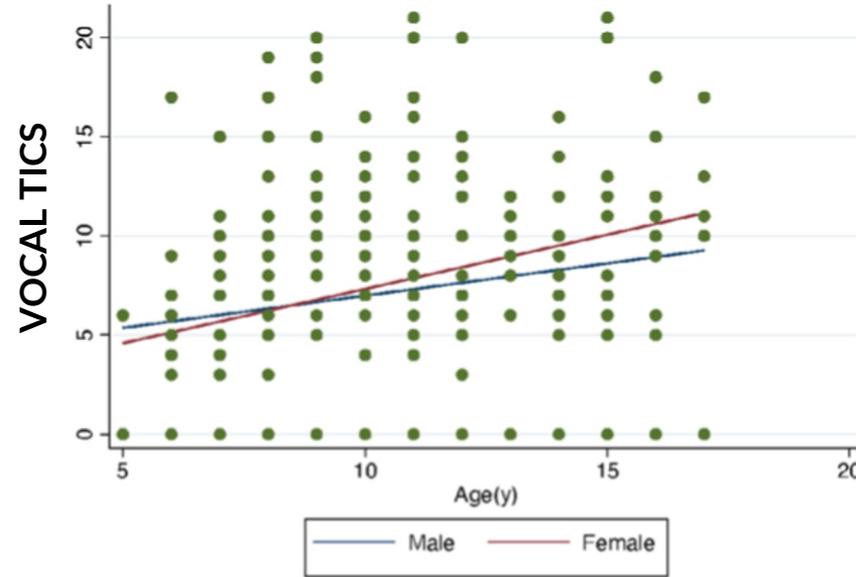
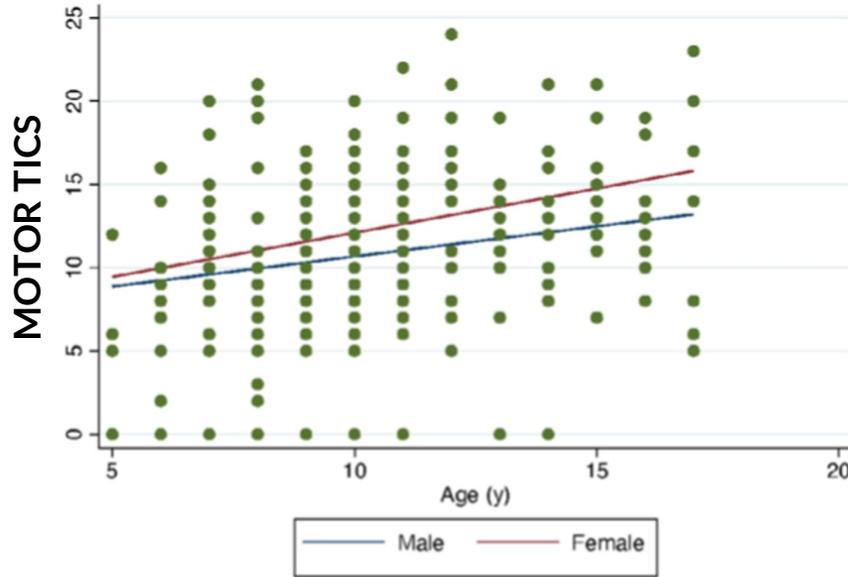
JOSEPH GIRGIS<sup>1</sup> | DAVIDE MARTINO<sup>2</sup> | TAMARA PRINGSHEIM<sup>2,3</sup> 

- Cross-sectional study in 270 children and adolescents (aged 5-17y, mean 10y 6mo), 212 males and 58 females
- **Objective:** to examine differences in tic severity and comorbidity profiles between the sexes

**Table 2:** Average age, age at onset, and scale scores

Scale	Males (n=212) Mean (SD)	Females (n=58) Mean (SD)	t-test p
Age at evaluation, y:mo	10:5 (2:10)	10:10 (3:7)	0.33
Age at tic onset, y:mo	6:6 (2:5)	6:4 (3:1)	0.78
<u>YGTSS – total motor</u>	10.81 (4.57)	12.55 (5.35)	<b>0.01</b>
YGTSS – total vocal	7.11 (5.50)	7.79 (5.29)	0.40
YGTSS – total tic (motor + vocal)	17.93 (8.36)	20.33 (9.10)	0.06
YGTSS – impairment rating	15 (12.60)	18.47 (13.06)	0.07
<u>YGTSS – global severity score</u>	32.66 (18.15)	38.79 (20.49)	<b>0.03</b>

# INCREASED SYMPTOM SEVERITY WITH AGE



- **Females:** higher motor tic severity ( $p=0.025$ ), tic-related impairments ( $p=0.051$ ), and global severity ( $p=0.045$ ) at all ages.
- **Females:** increased symptom severity with age > males, for all the measurements except for tic-related impairments.
- **Females:** more severe vocal tics at an older age ( $p=0.077$ ).

# Have We Forgotten What Tics Are? A Re-Exploration of Tic Phenomenology in Youth with Primary Tics

Christelle Nilles MD, Davide Martino MD, PhD, Julian Fletcher BA, Tamara Pringsheim MD ✉

First published: 21 February 2023 | <https://doi.org/10.1002/mdc3.13703>

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*N=203 children and adolescents with primary tic disorders; 76.4% males; mean age: 10.7y.*

**In comparison with young males, young females had:**

**1) More simple tics:** nose movements (OR=2.87, p=0.003), shoulder shrugs (OR=2.52, p=0.010), simple leg/foot/toe movements (OR=2.11, p=0.040), sniffing tics (OR=2.21, p=0.027) and grunting tics (OR=4.10, p=0.016)

**2) Higher frequency** (p=0.032) **and intensity** (p=0.006) **of motor tics** and **greater tic-related impairment** (p=0.045).



# SEX DIFFERENCES IN TICS IN CHILDHOOD: HYPOTHESES

- Differences in tic awareness and self-report of tics?
- Increased levels of stress and depression in females?
- Different phenotype and natural history of tics based on sex?



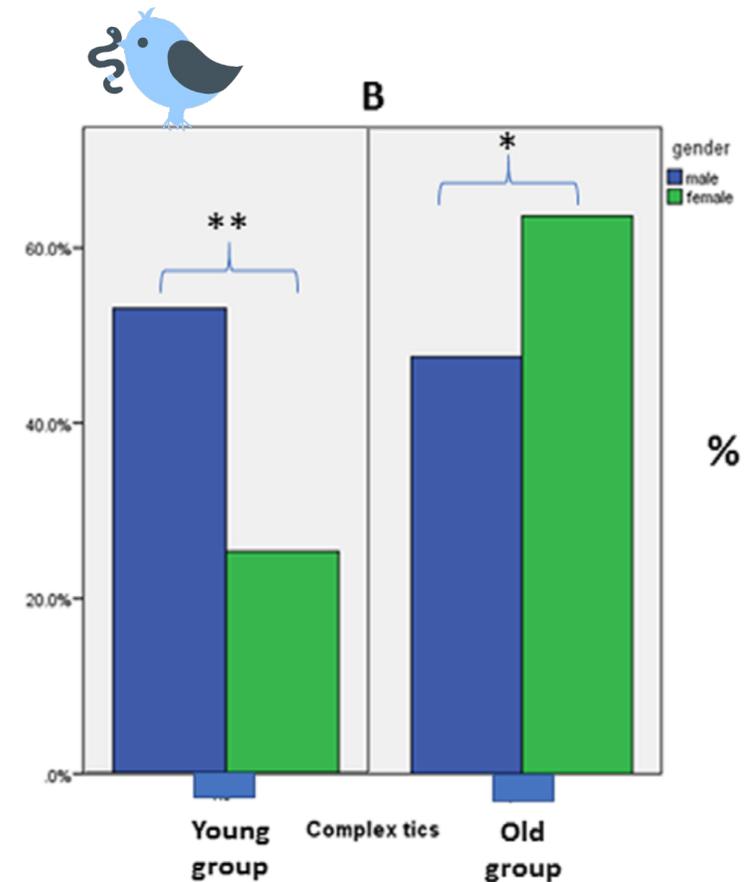
# DIVERGENT DATA?

## Sex differences in patients with Tourette syndrome

José Fidel Baizabal-Carvallo<sup>1,2\*</sup>  and Joseph Jankovic<sup>1</sup>

<sup>1</sup>Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA and <sup>2</sup>Department of Sciences and Engineering, University of Guanajuato, Guanajuato, México

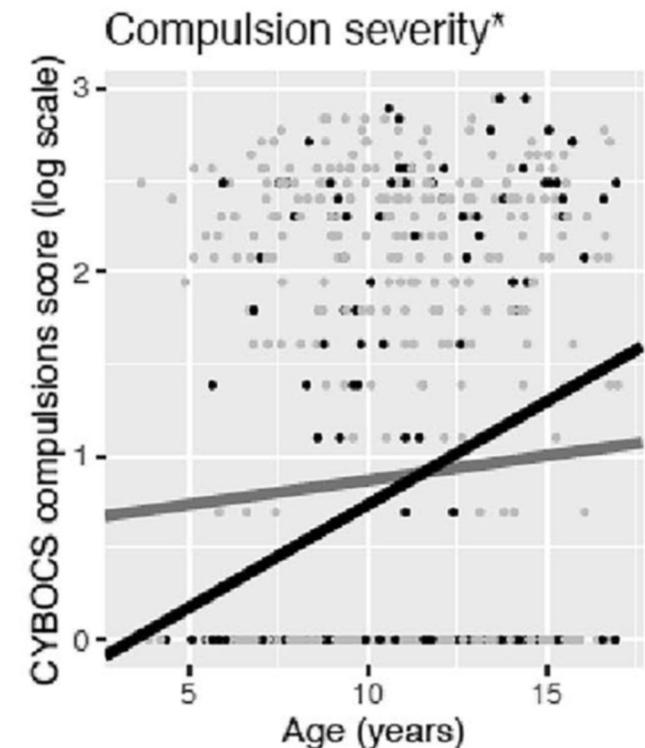
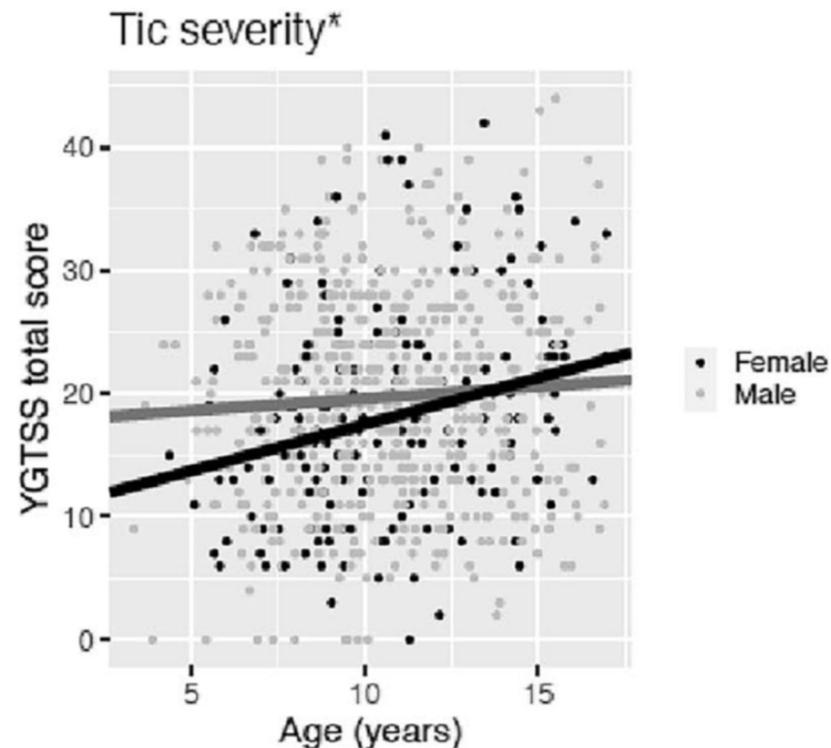
- N=201 individuals (age 4-65 years) with tic disorders
- Males < 18 years had a greater complexity and severity of tics than females (p=0.049). These differences were not present in subjects > 18yr.
- Only females had increased tic complexity and severity in adulthood compared to childhood.



# A DIFFERENT EVOLUTION BY SEX

## EMTICS study<sup>1</sup> : 16 different centres

- n=709 children and adolescents with TS/persistent tic disorders
- **Greater tic severity in boys.**
- **But higher tic severity in girls with age (and compulsions).**



<sup>1</sup>Garcia-Delgar et al, 2021.

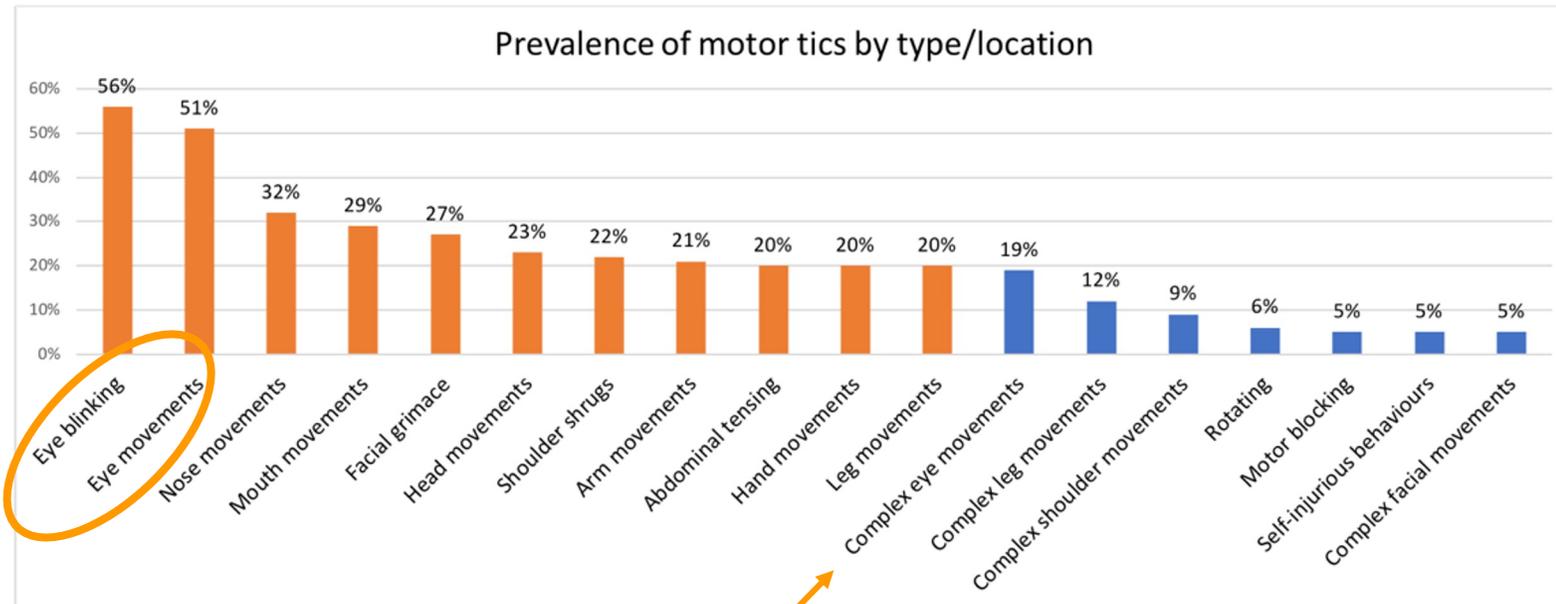
# Exploration of sex differences in tic disorders in adulthood



# THE CALGARY AND PARIS (CAP) ADULT TIC REGISTRY



- **N=164 adults** with tic disorders; mean age: 32.9y in French participants, 31.7y in Canadian participants. 88% had TS.
- **Sex ratio 1.9 males: 1 female.**
- **51% anxiety, 36% depression, 30% had ADHD, 21% OCD.**





# THE CAP ADULT TIC REGISTRY: SEX DIFFERENCES

- Canadian **women**: more simple hand tics than men (OR=3.0, p=0.03)
- Canadian **women**:
  - Greater complexity of motor tics (p=0.048)
  - Greater motor tic score (p=0.03)
  - Greater tic-related impairment (p=0.003)
- Canadian **women**: more anxiety disorders (OR=3.2, p=0.01).
- French **women**: more OCD (OR=4.8, p=0.02).

## *Similar to a study in 75 adults with TS from a university-based clinic <sup>1</sup>*

- **Women**: higher YGTSS motor tic severity scores (p=0.036) and greater TS-related impairment > men
- **Women**: expansion of the number of body regions affected by tics & tic worsening as opposed to tic improvement in adulthood > men

<sup>1</sup>Lichter et al, 2015

# EXAMINATION OF THE MORE EVEN SEX RATIO IN ADULTS WITH TICS

## *More persistent/severe forms of TS in females?*

- Underdiagnosis /delayed diagnosis of TS in girls in childhood?
- Women seek health-care more often in adulthood?
  - due to higher tic-related impairment
  - or higher levels of distress/depression/anxiety?

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- Santangelo et al, 1994: females **older** than males at diagnosis.
- 2023: **no difference in age at onset/presentation** in our Registry in adults and children.
- Garcia-Delgar et al, 2021: higher severity of tics in young boys could **facilitate TS detection**.
- Girgis et al, 2021: Females were less likely to be diagnosed with **ADHD** (OR=0.48).
- Lewin et al, 2012: 1/3 women first received treatment **>18 years**.

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○ **due to higher tic-related impairment?**

○ or higher levels of distress/depression/anxiety?

**1**

***Cross-sectional study in 185 females and 275 males with tic disorders, aged 18-79 years***<sup>1</sup>

- Women: greater tic-related interference in their social lives > men.

**2**

***Recent cross-sectional study in 132 adolescents with TS (49 females)***<sup>2</sup>

- Tic- and non-tic-related impairment were lower in older boys, but not in older girls.

# EXAMINATION OF THE MORE EVEN SEX RATIO IN ADULTS WITH TICS

## ***More persistent/severe forms of TS in females?***

- Underdiagnosis /delayed diagnosis of TS in girls in childhood?
- Women seek health-care more often in adulthood?
  - due to higher tic-related impairment?
  - **or higher levels of distress/depression/anxiety?**

- Females with TS: more likely than males to have depression and anxiety.<sup>1</sup>
- **Tic severity correlates with comorbid depression** in children and adolescents <sup>2</sup> and in adults <sup>3</sup> and **with comorbid anxiety.** <sup>4</sup>
  - *The high prevalence of mood and anxiety disorders in women with TS may play a role in the severity of their tics.*

# Substrates underlying sex differences in TS



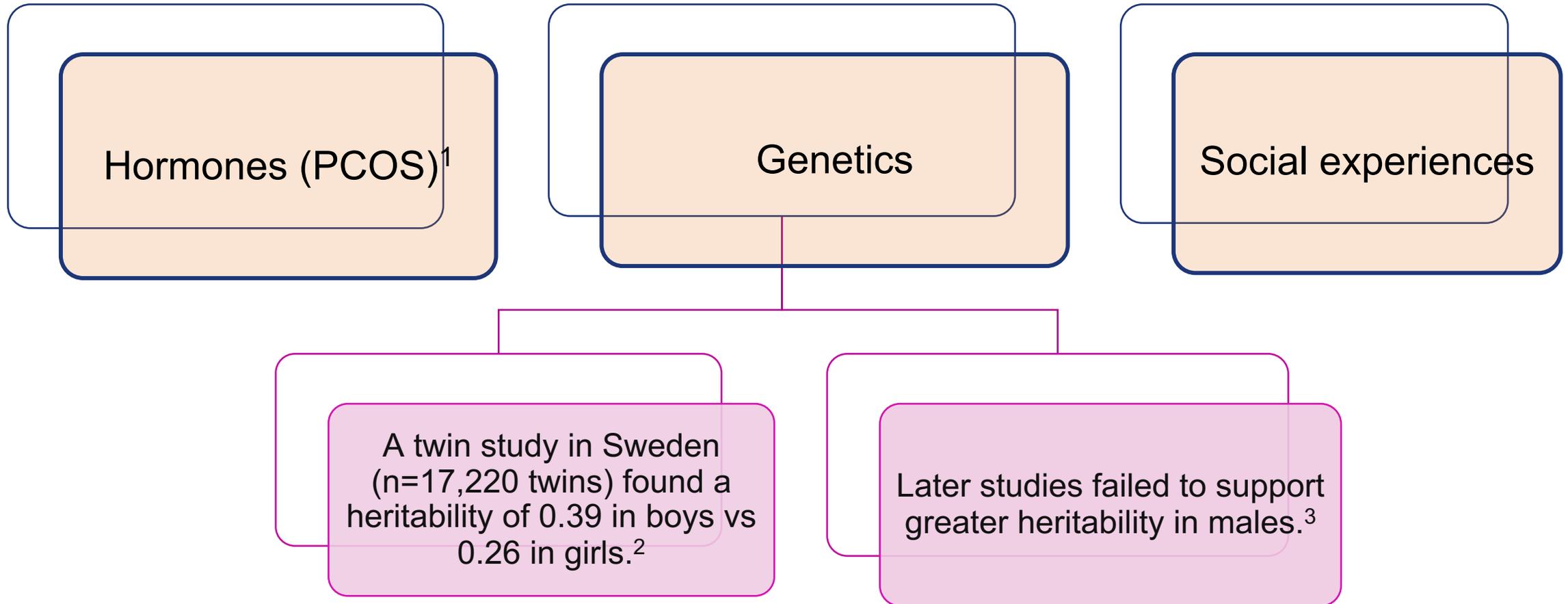
# A DIFFERENT BRAIN IN TS?



- Brain imaging studies have suggested that **males with TS might have more widespread brain alterations than females with TS** compared with typically developing peers.<sup>1</sup>
  - Altered cortical and callosal thickness and basal ganglia volume in childhood.<sup>2,3</sup>
  - ↓ cortical thickness in prefrontal, orbitofrontal and parietal regions.<sup>4</sup>

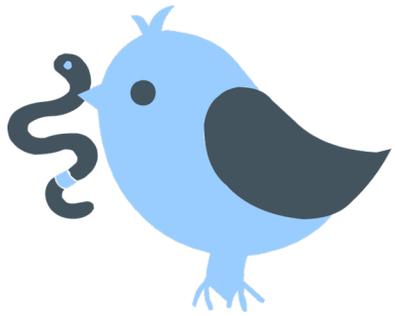
<sup>1</sup>Bölte et al, 2023; <sup>2</sup>Garris et al, 2021; <sup>3</sup>Pinares-Garcia et al, 2018; <sup>4</sup>Fahim et al, 2010

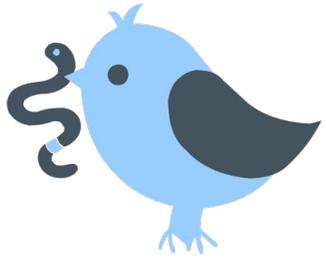
# OTHER SEX-RELATED FACTORS INFLUENCING TIC DISORDERS



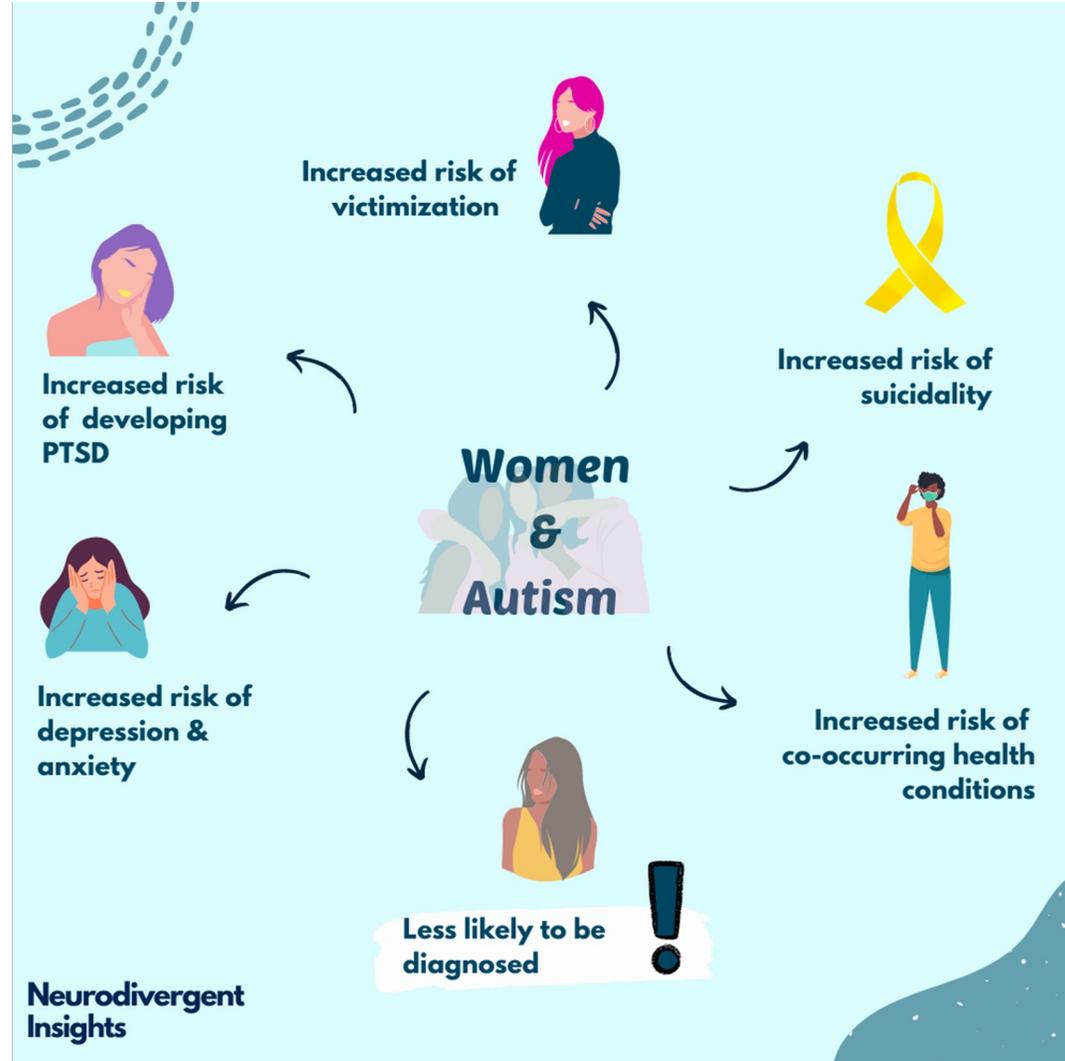
<sup>1</sup>Dubey et al, 2021; <sup>2</sup>Anckarsäter et al, 2011; <sup>3</sup>Qi et al, 2017

# Evidence from other neurodevelopmental disorders

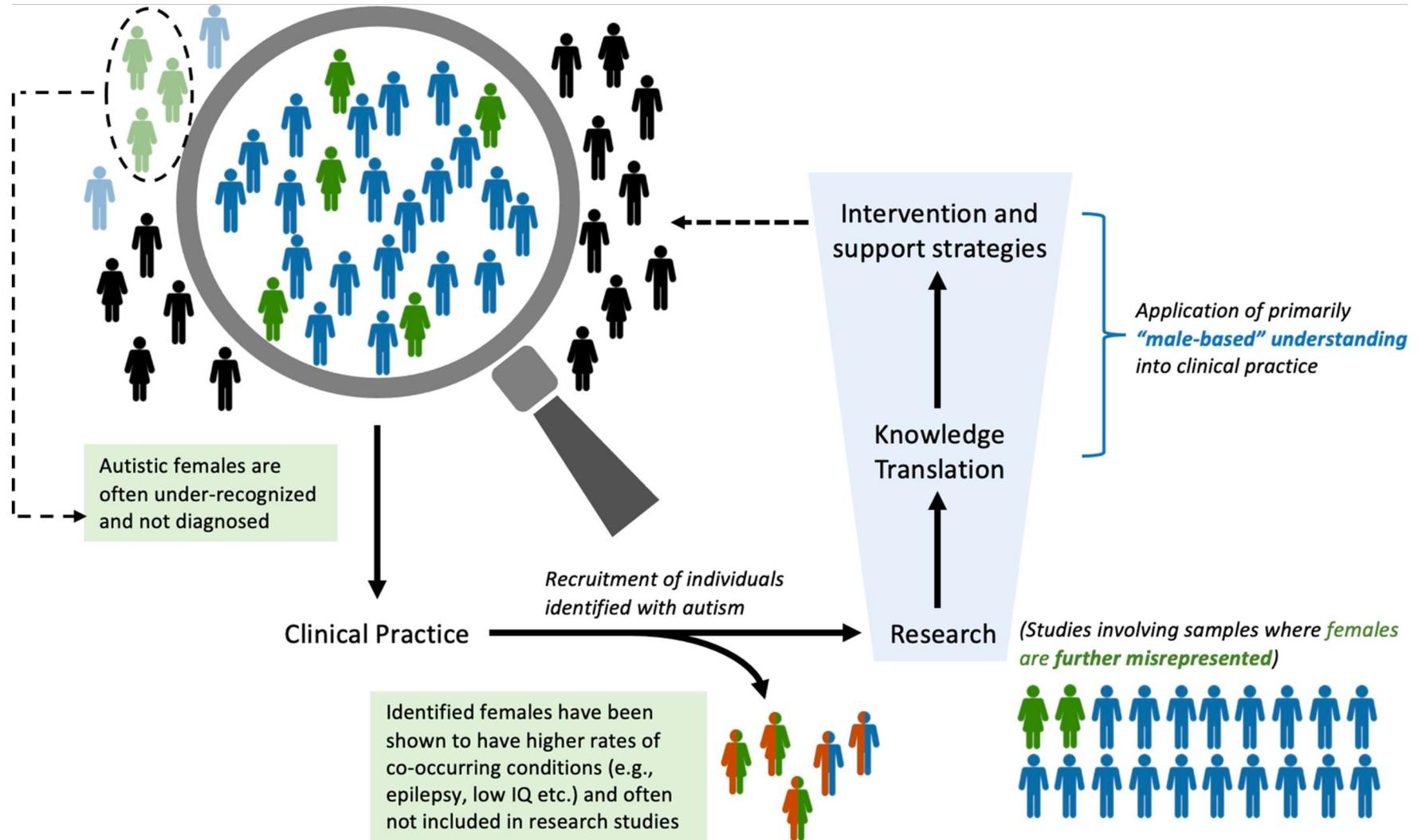


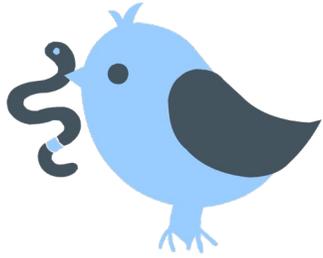


# Autism



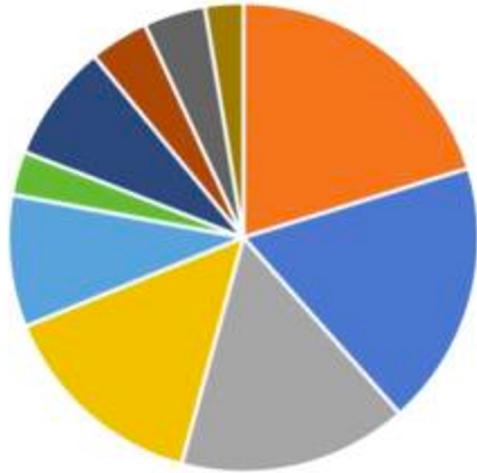
# The "Male-Lens" in Clinical Practice and Research in Autism



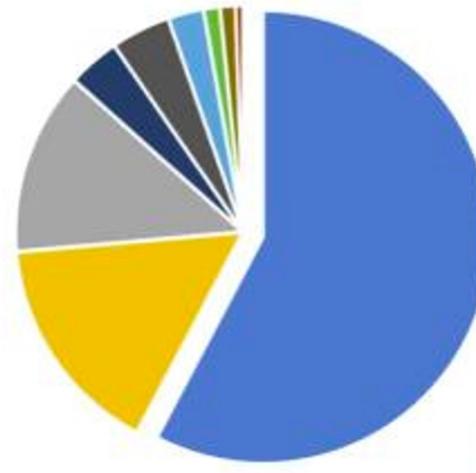


# The "Male-Lens"

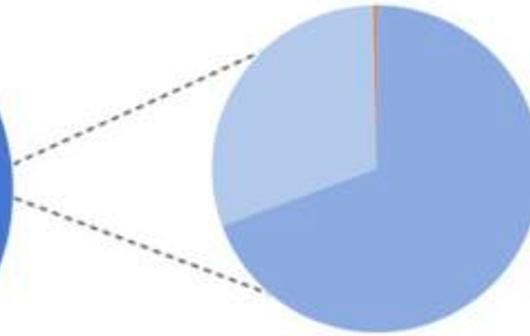
**Review – 494  
(Secondary Articles)**



**Empirical – 1,916  
(Primary Articles)**

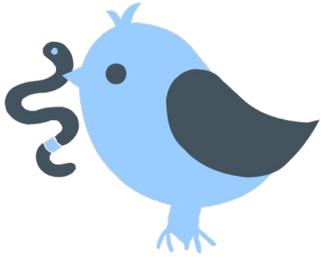


**Brain Structure & Function – 1,428**

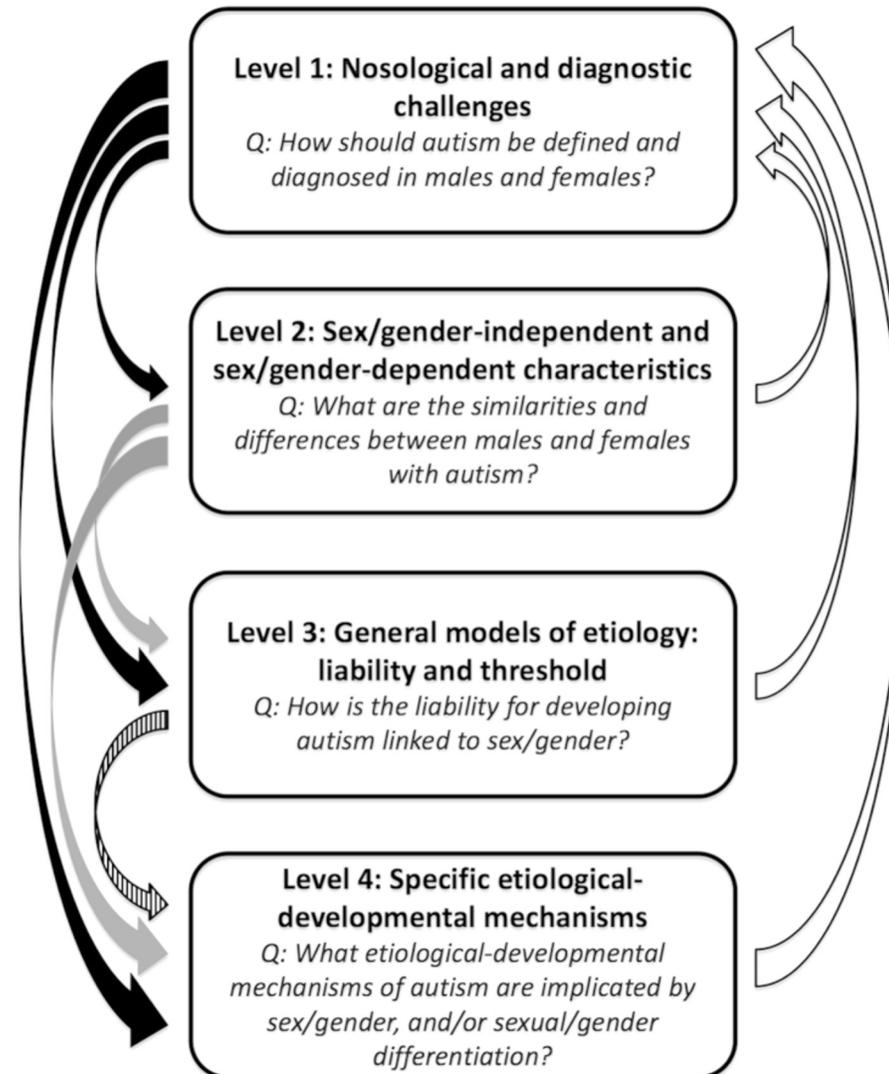


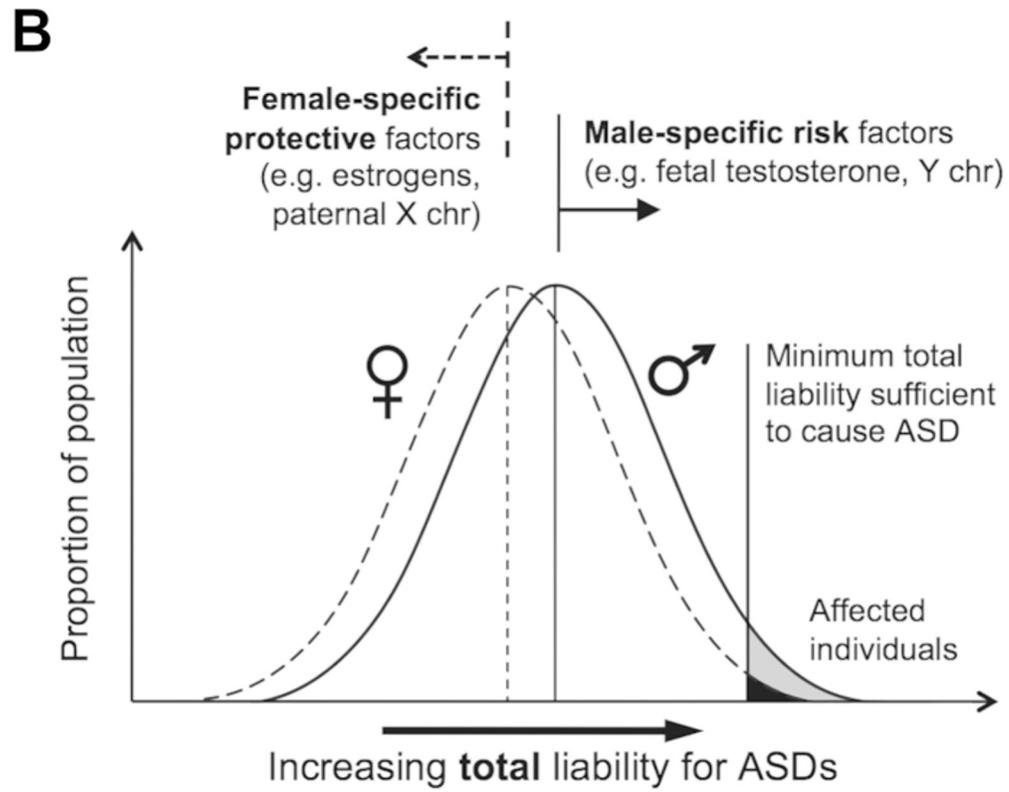
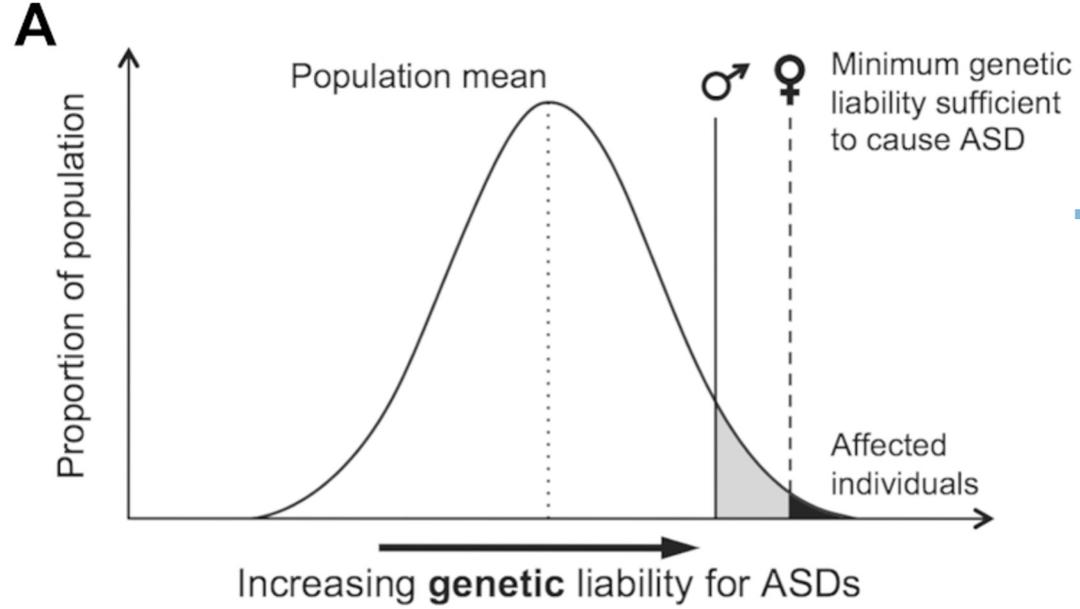
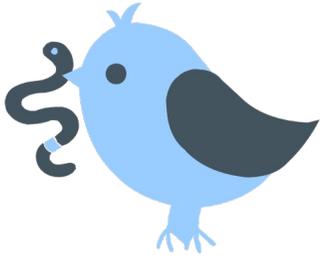
■ Both sexes (990)   
 ■ Male only (434)   
 ■ Female only (4)

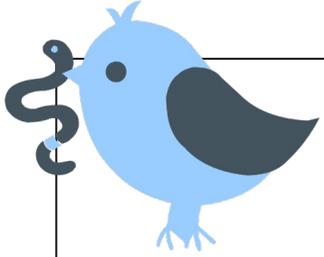
- |   |  |
|---|--|
| <span style="color: orange;">■</span> General (Review)              | <span style="color: green;">■</span> Environmental Factors         |
| <span style="color: blue;">■</span> Brain Structure & Function      | <span style="color: darkblue;">■</span> Prenatal/Perinatal Factors |
| <span style="color: grey;">■</span> Genetics                        | <span style="color: brown;">■</span> Immunology                    |
| <span style="color: yellow;">■</span> Behaviour & Cognition         | <span style="color: darkgrey;">■</span> Biochemistry               |
| <span style="color: lightblue;">■</span> Endocrine/Hormonal Factors | <span style="color: olive;">■</span> Clinical Trial/Intervention   |



# Research questions







## Study definitions of 'sex' versus 'gender'

	N	Definition provided?	Where a definition was provided, was the term defined/used correctly?	Proxy measure provided for sex and/or gender?
Studies using „sex” term	57	33.3% Yes (N=19), 66.7% No (N=38)	100% Yes (N=19)	3.5% Yes (N=2); participants were assigned to the female/girl or male/boy group based on parent-report of biological sex designated at birth  96.5% No (N=55)
Studies using „gender” term	12	No (12, 100%)	NA – no definition provided	None for all studies



# Symptomatology: behaviors

Domain	Characteristics More Often Present in Females Than in Males
Social interaction	<p>Greater awareness of the need for social interaction</p> <p>Desire to interact with others</p> <p>Passivity (a “loner”), often perceived as “just being shy”</p> <p>Tendency to imitate others (copy, mimic, or mask) in social interactions, which may be exhausting</p> <p>Tendency to “camouflage” difficulties by masking and/or developing compensatory strategies</p> <p>One or few close friendships</p> <p>Tendency to be “mothered” in a peer group in primary school but often bullied in secondary school</p>
Communication	<p>Better linguistic abilities developmentally</p> <p>Better imagination (fantasizes and escapes into fiction and pretend to play, but is prone to being nonreciprocal, scripted, and overly controlled)</p>
Restricted, repetitive patterns of behavior, interests, or activities	<p>Restricted interests tend to involve people/animals rather than objects/things, which may be less recognized as related to autism</p>
Other	<p>Tendency to be perfectionist, very determined</p> <p>Tendency to be controlling (in play with peers)</p> <p>High (passive) demand avoidance</p> <p>Tendency to have episodes of eating problems</p>

Beggatio et al. Gender differences in autism spectrum disorders: Divergence among specific core symptoms. *Autism Res.* 2017 Apr;10(4):680-689. doi: 10.1002/aur.1715. Epub 2016 Nov 3.

## How females with autism spectrum disorder differ from males

Researchers from the Lurie Center for Autism at Massachusetts General Hospital recently published an article advocating for greater awareness of how females with autism spectrum disorder (ASD) differ from males. Their goal is to improve early detection rates and help guide new treatment strategies.

### IMAGINATIVE PLAY AND EMOTIONAL WORDS

Females with ASD tend to engage in pretend and imaginative play from a young age. Their speech also contains more vocabulary words related to emotions in comparison to males.



### DIFFERENT INTERESTS

Many females with ASD have intense, highly focused interests related to people and animals (such as celebrities and pets) as opposed to their male counterparts, who tend to be more interested in objects.



### SOCIAL INTERACTION

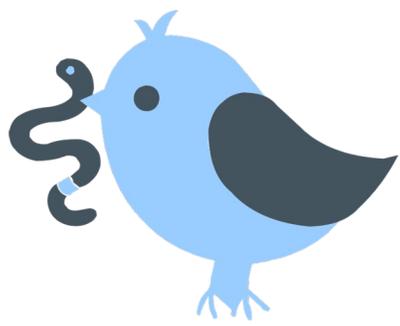
Females with ASD have a greater awareness of and desire for social interaction and often develop one or two close friends. They may camouflage their social difficulties through coping strategies such as mimicking the facial expressions and gestures of others.



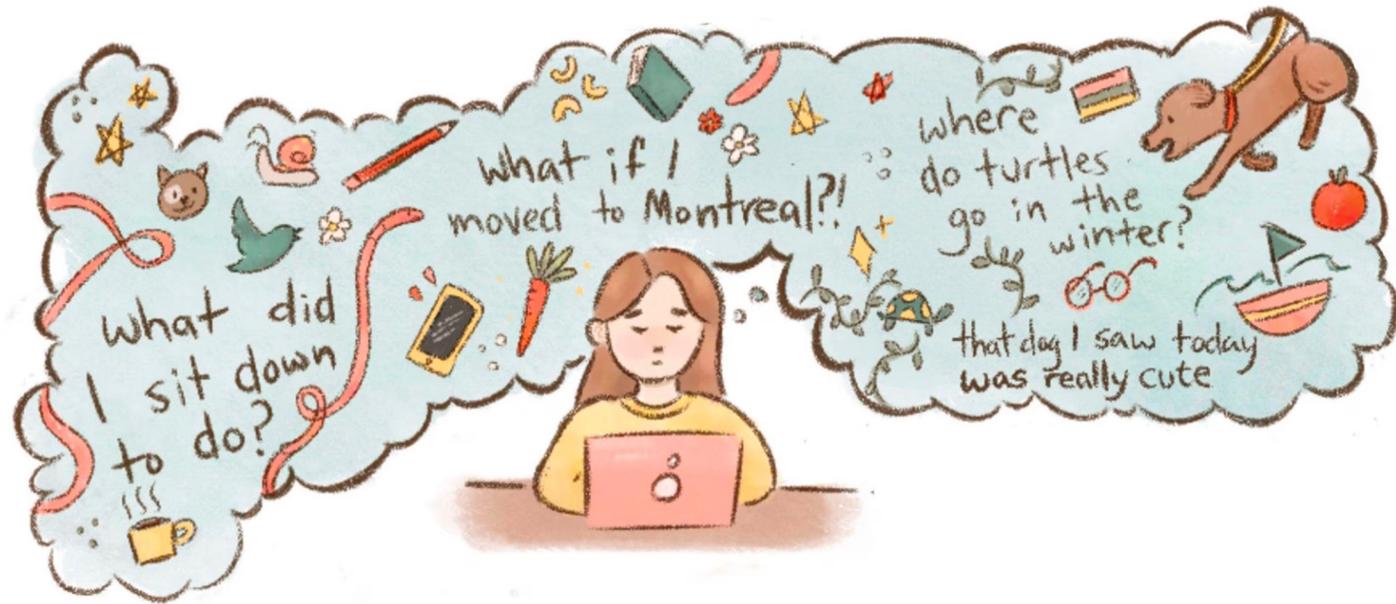
### INTERNALIZING DISORDERS

Females with ASD have higher rates of internalizing psychiatric disorders such as anxiety, depression and eating disorders. These may be triggered or exacerbated by pressure to live up to feminine societal gender norms regarding children, relationships, etc.





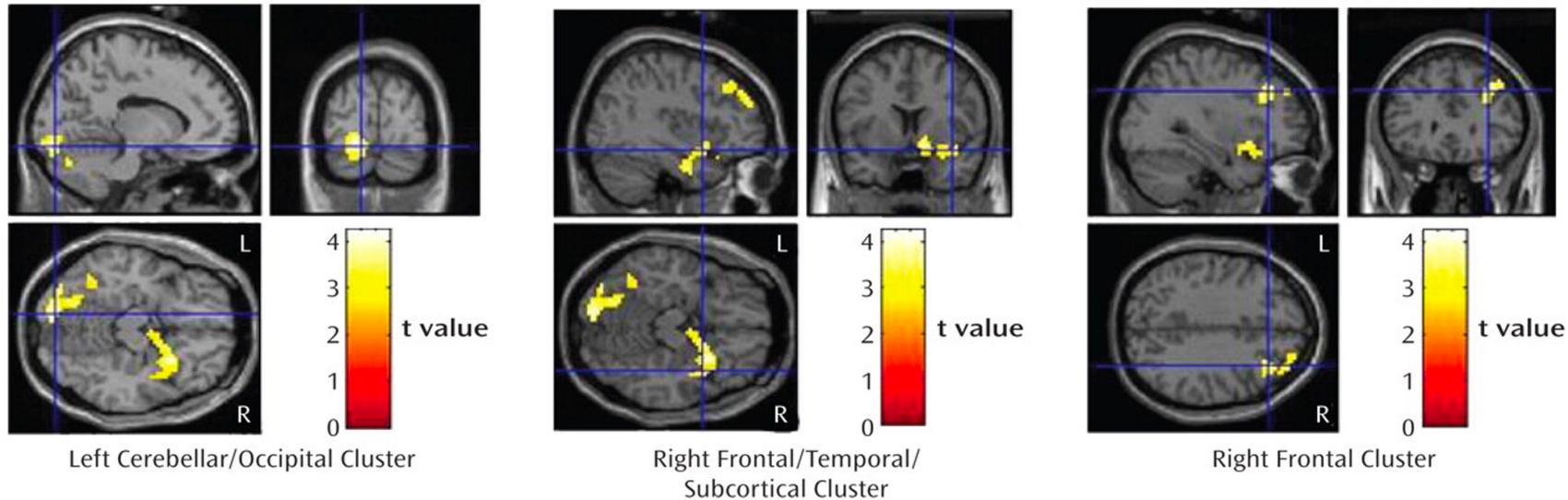
# ADHD



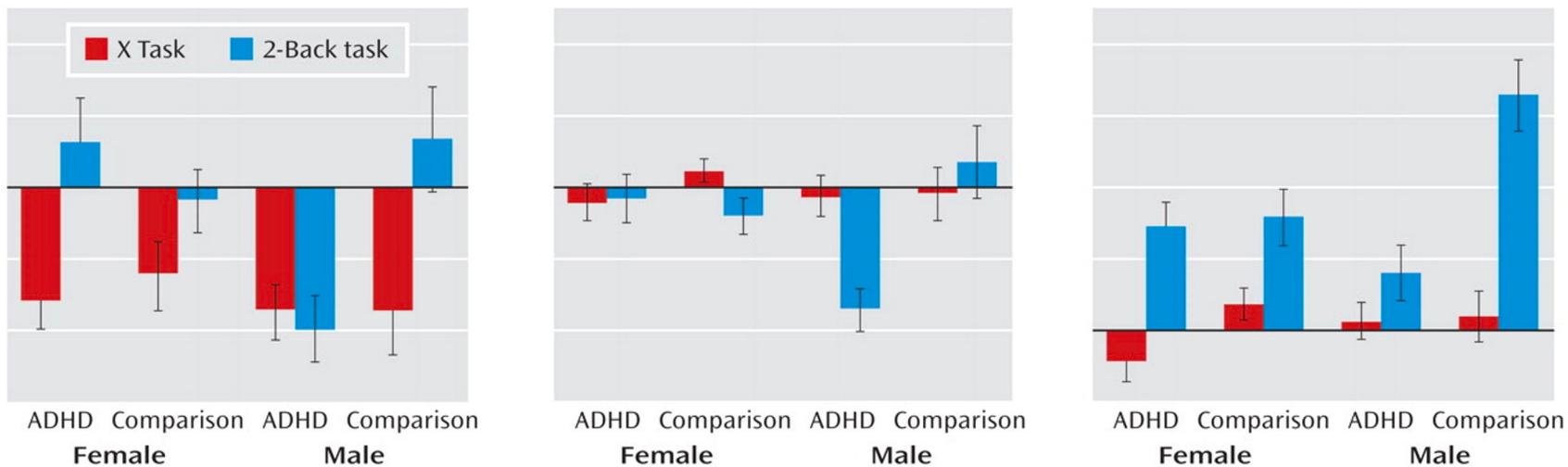


# Biological substrates

Group-by-Sex Interaction (comparison men – ADHD men) > (comparison women – ADHD women)<sup>a</sup>



Change in BOLD Signal From Baseline During Working Memory Task (arbitrary units, mean±SD)<sup>b</sup>



Symptoms may be exacerbated by **hormonal changes** during menstrual cycle, pregnancy and menopause.

Symptom severity may be **lower**

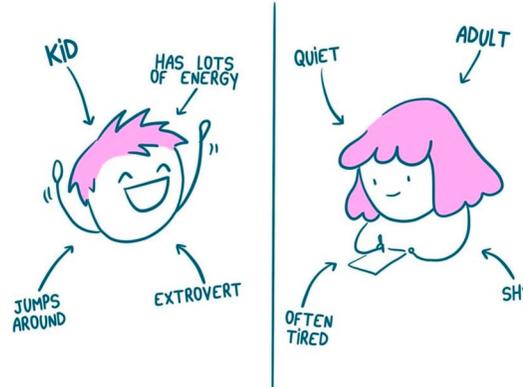
Symptoms are **pervasive** and **impairing** rather than transient or fluctuating

**Gender-based biases** in teachers and parents appear to affect referral likelihood

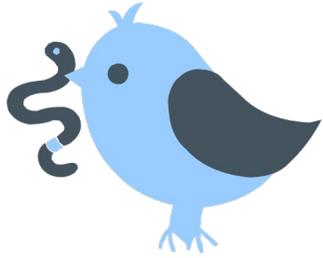
### ADHD STEREOTYPES:

YOUNG BOY JUMPING AROUND

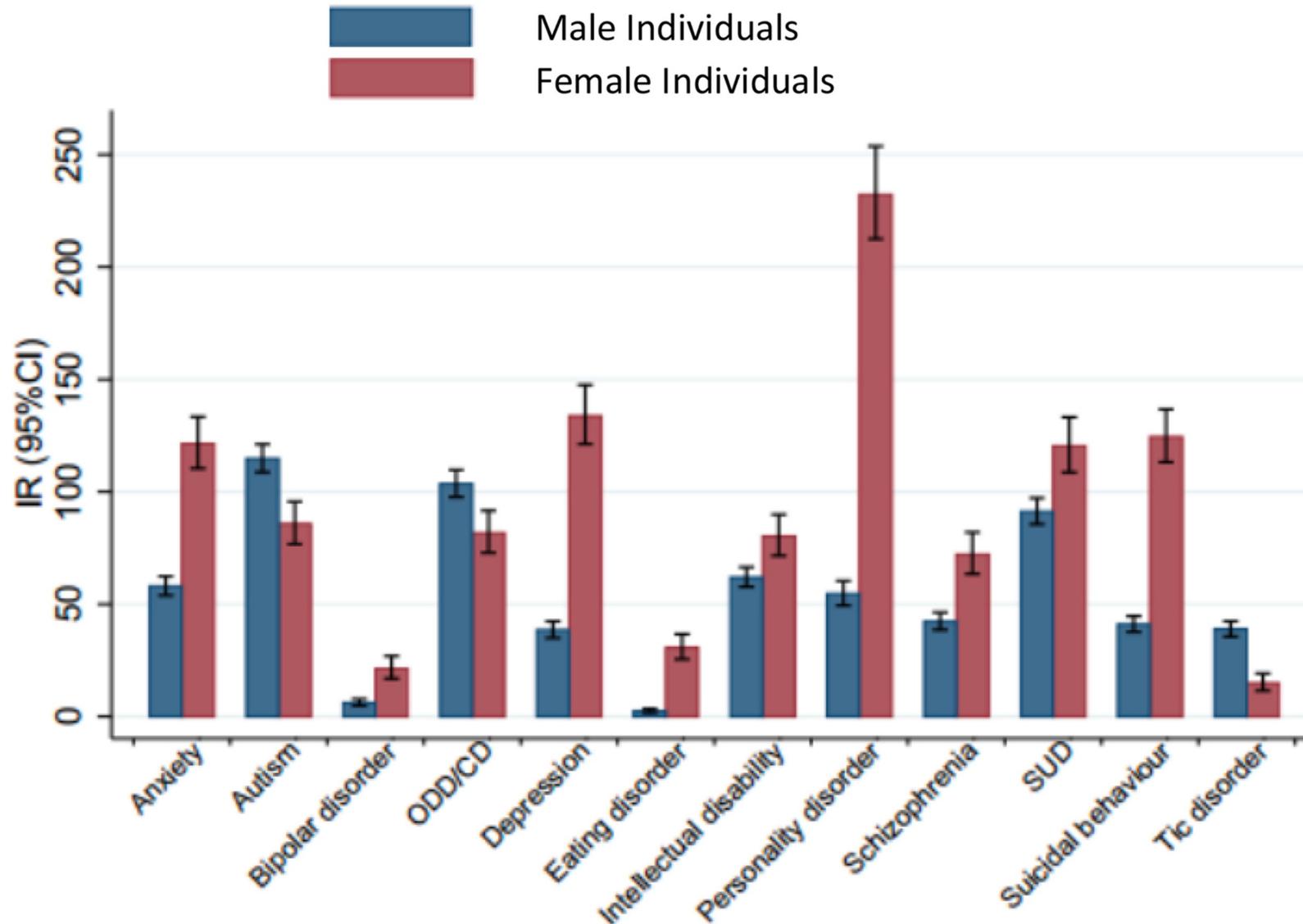
QUIET AND SHY GIRL



ADHD symptoms may become more obvious **later** in females, often during periods of social or educational transition.



# Comorbidity

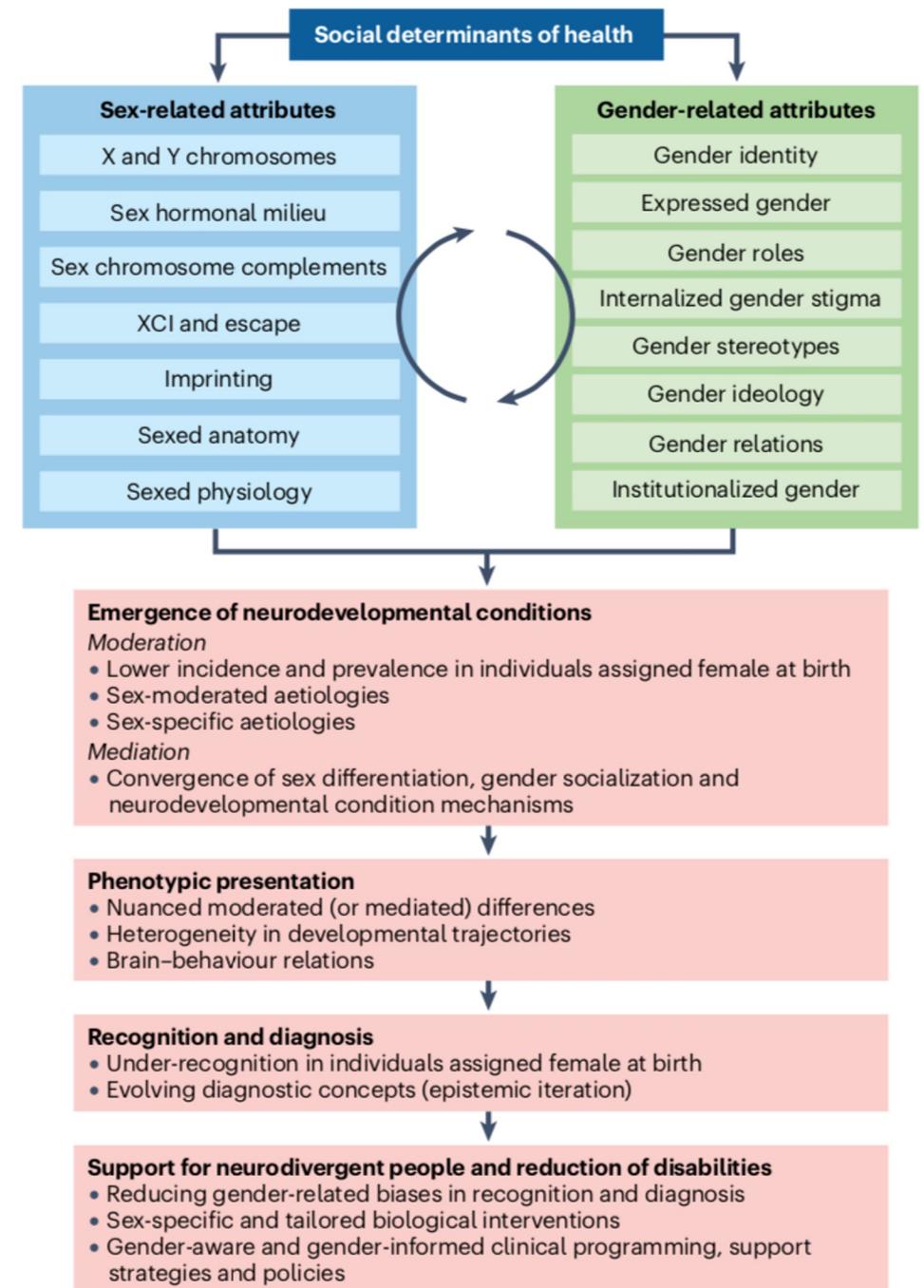


Ottosen et al. Sex Differences in Comorbidity Patterns of Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry*. 2019 Apr;58(4):412-422.e3. doi: 10.1016/j.jaac.2018.07.910. Epub 2019 Jan 8.

# Sex and gender in neurodevelopmental conditions

Sven Bölte<sup>1,2,3</sup>✉, Janina Neufeld<sup>1,4</sup>, Peter B. Marschik<sup>1,5,6</sup>, Zachary J. Williams<sup>7,8,9</sup>, Louise Gallagher<sup>10,11</sup>  
& Meng-Chuan Lai<sup>11,12,13</sup>✉

*Explores the sex and gender-related factors (biological, behavioural) that influence neurodevelopmental conditions.*

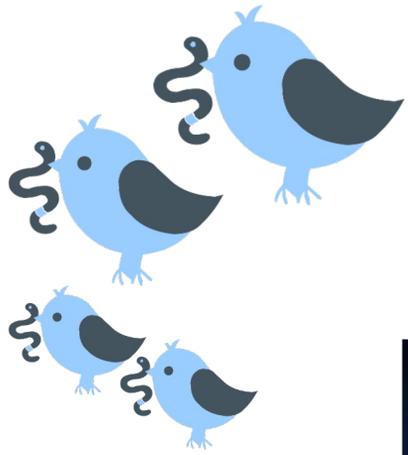


**Fig. 1 | Why are sex and gender important for neurodevelopmental conditions?**

# KEY MESSAGES & FUTURE RESEARCH

- Overall, although findings on sex differences before age 18 varied, there is accumulating evidence that **females may have slightly greater tic severity and tic-related impairment with age.**
- **Sex seems to contribute to the variability in TS** via genetics, endocrinological factors, brain structure, behaviours, comorbidities...
- Evidence from other neurodevelopmental disorders such as ADHD and autism support that males and females have **different phenotype.**
- **Future research:** exploring the female experience of tic disorders in childhood and adulthood; considering sex but also gender in studies; examination of the association between tic severity and tic-related impairment in women versus men.





# THANK YOU FOR YOUR ATTENTION

Prof. Tamara Pringsheim



Mr Julian Fletcher



Dr Andreas Hartmann



Dr Yulia Worbe



Dr Davide Martino



Prof. Emmanuel Roze



Supported by AFSGT