Sex, Gender, and Autism: An Update

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Disclosure

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Sex ≠ Gender

Multi-component constructs

**Sometimes non-binary, and are often multi-categorical or continuous**

Caveat – current autism (& clinical/neuroscience) research mostly still treats them as a single, binary variable – ***a proxy measure***

Mitigation –
- ✓ **Measuring these complexities to capture more variances**
- ✓ **Measuring the specific components that are relevant**
- ✓ **Modelling/analyzing their effects separately and jointly**

Sex/gender differences in the human autistic brains: A systematic review of 20 years of neuroimaging research

Kelly Mo [a,b], Tara Sadoway [c], Sarah Bonato [b], Stephanie H. Ameis [a,b,d,e],
Evdokia Anagnostou [a,f,g], Jason P. Lerch [a,h,i], Margot J. Taylor [a,i,j], Meng-Chuan Lai [a,b,d,e,i,k,l,*]
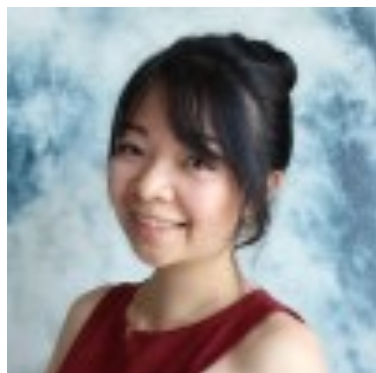
Brain Structure & Function – 1,428

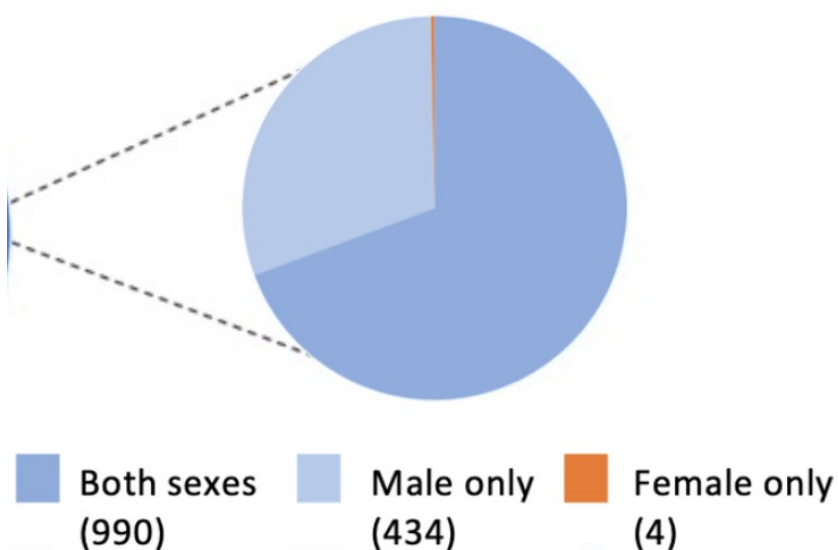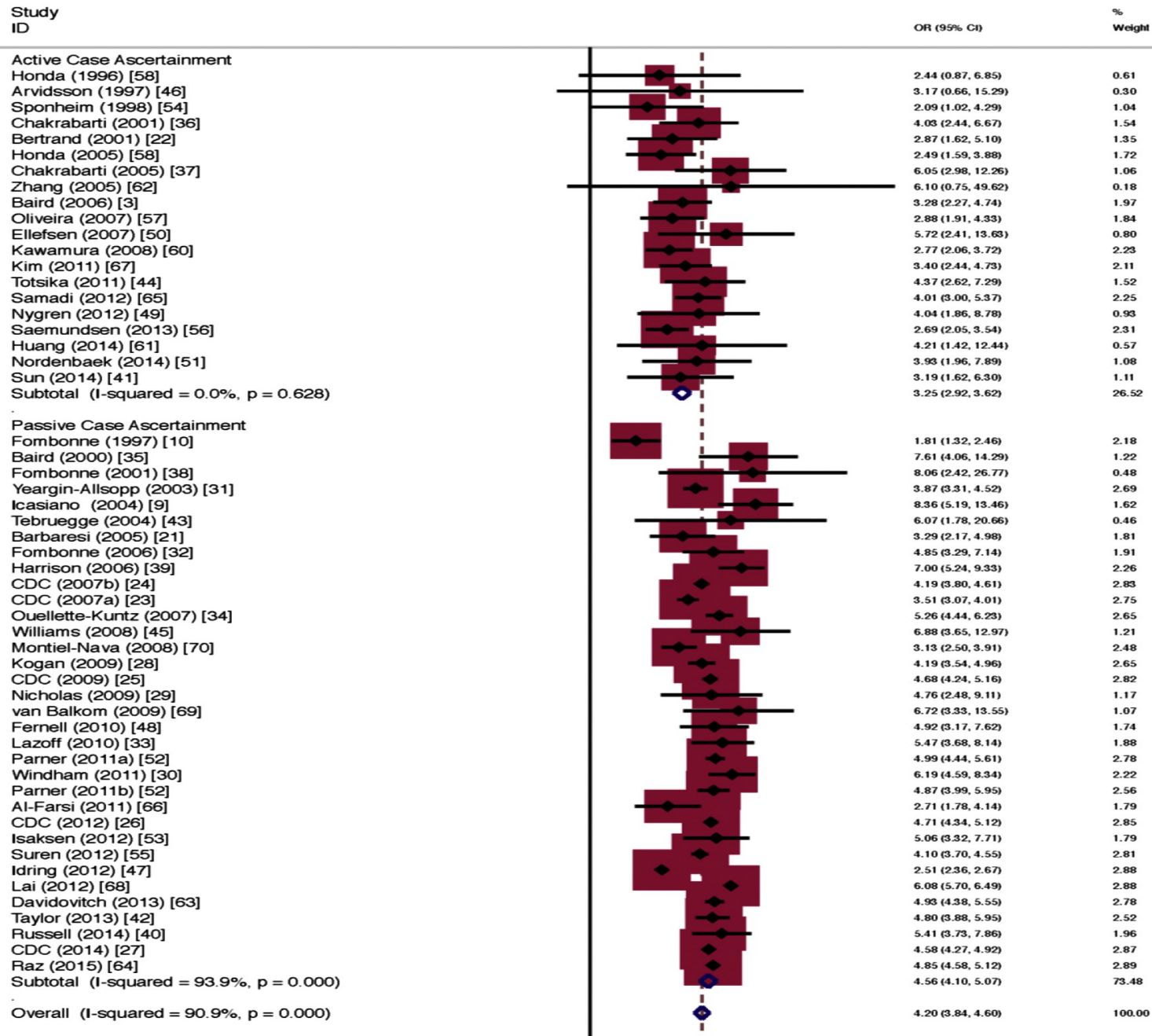Both sexes (990) Male only (434) Female only (4)

Table 1
Summary of 'sex' and 'gender' definitions.

	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%)	N/A – no definition provided	None for all studies

Study ID | OR (95% CI) | % Weight

Active Case Ascertainment
Honda (1996) [58] — 2.44 (0.87, 6.85) — 0.61
Arvidsson (1997) [46] — 3.17 (0.66, 15.29) — 0.30
Sponheim (1998) [54] — 2.09 (1.02, 4.29) — 1.04
Chakrabarti (2001) [36] — 4.03 (2.44, 6.67) — 1.54
Bertrand (2001) [22] — 2.87 (1.62, 5.10) — 1.35
Honda (2005) [58] — 2.49 (1.59, 3.88) — 1.72
Chakrabarti (2005) [37] — 6.05 (2.98, 12.26) — 1.06
Zhang (2005) [62] — 6.10 (0.75, 49.62) — 0.18
Baird (2006) [3] — 3.28 (2.27, 4.74) — 1.97
Oliveira (2007) [57] — 2.88 (1.91, 4.33) — 1.84
Ellefsen (2007) [50] — 5.72 (2.41, 13.63) — 0.80
Kawamura (2008) [60] — 2.77 (2.06, 3.72) — 2.23
Kim (2011) [67] — 3.40 (2.44, 4.73) — 2.11
Totsika (2011) [44] — 4.37 (2.62, 7.29) — 1.52
Samadi (2012) [65] — 4.01 (3.00, 5.37) — 2.25
Nygren (2012) [49] — 4.04 (1.86, 8.78) — 0.93
Saemundsen (2013) [56] — 2.69 (2.05, 3.54) — 2.31
Huang (2014) [61] — 4.21 (1.42, 12.44) — 0.57
Nordenbaek (2014) [51] — 3.93 (1.96, 7.89) — 1.08
Sun (2014) [41] — 3.19 (1.62, 6.30) — 1.11
Subtotal (I-squared = 0.0%, p = 0.628) — 3.25 (2.92, 3.62) — 26.52

Passive Case Ascertainment
Fombonne (1997) [10] — 1.81 (1.32, 2.46) — 2.18
Baird (2000) [35] — 7.61 (4.06, 14.29) — 1.22
Fombonne (2001) [38] — 8.06 (2.42, 26.77) — 0.48
Yeargin-Allsopp (2003) [31] — 3.87 (3.31, 4.52) — 2.69
Icasiano (2004) [9] — 8.36 (5.19, 13.46) — 1.62
Tebruegge (2004) [43] — 6.07 (1.78, 20.66) — 0.46
Barbaresi (2005) [21] — 3.29 (2.17, 4.98) — 1.81
Fombonne (2006) [32] — 4.85 (3.29, 7.14) — 1.91
Harrison (2006) [39] — 7.00 (5.24, 9.33) — 2.26
CDC (2007b) [24] — 4.19 (3.80, 4.61) — 2.83
CDC (2007a) [23] — 3.51 (3.07, 4.01) — 2.75
Ouellette-Kuntz (2007) [34] — 5.26 (4.44, 6.23) — 2.65
Williams (2008) [45] — 6.88 (3.65, 12.97) — 1.21
Montiel-Nava (2008) [70] — 3.13 (2.50, 3.91) — 2.48
Kogan (2009) [28] — 4.19 (3.54, 4.96) — 2.65
CDC (2009) [25] — 4.68 (4.24, 5.16) — 2.82
Nicholas (2009) [29] — 4.76 (2.48, 9.11) — 1.17
van Balkom (2009) [69] — 6.72 (3.33, 13.55) — 1.07
Fernell (2010) [48] — 4.92 (3.17, 7.62) — 1.74
Lazoff (2010) [33] — 5.47 (3.68, 8.14) — 1.88
Parner (2011a) [52] — 4.99 (4.44, 5.61) — 2.78
Windham (2011) [30] — 6.19 (4.59, 8.34) — 2.22
Parner (2011b) [52] — 4.87 (3.99, 5.95) — 2.56
Al-Farsi (2011) [66] — 2.71 (1.78, 4.14) — 1.79
CDC (2012) [26] — 4.71 (4.34, 5.12) — 2.85
Isaksen (2012) [53] — 5.06 (3.32, 7.71) — 1.79
Suren (2012) [55] — 4.10 (3.70, 4.55) — 2.81
Idring (2012) [47] — 2.51 (2.36, 2.67) — 2.88
Lai (2012) [68] — 6.08 (5.70, 6.49) — 2.88
Davidovitch (2013) [63] — 4.93 (4.38, 5.55) — 2.78
Taylor (2013) [42] — 4.80 (3.88, 5.95) — 2.52
Russell (2014) [40] — 5.41 (3.73, 7.86) — 1.96
CDC (2014) [27] — 4.58 (4.27, 4.92) — 2.87
Raz (2015) [64] — 4.85 (4.58, 5.12) — 2.89
Subtotal (I-squared = 93.9%, p = 0.000) — 4.56 (4.10, 5.07) — 73.48

Overall (I-squared = 90.9%, p = 0.000) — 4.20 (3.84, 4.60) — 100.00

Although overall ratio
4.20 (3.84 – 4.60) …

'Active' Case Ascertainment
3.25 (2.92 – 3.62)

'Passive' Case Ascertainment
4.56 (4.10 – 5.07)

Loomes et al., 2017, *JAACAP*

Why should we care about sex & gender in autism?

Clinical care (diagnosis, behavioural presentation, health status, supports)

Biological heterogeneity

Aetiologies

How do sex & gender modulate recognition, presentation, adaptation & developmental changes?

(How) Are the biological substrates of autism differ by sex & gender?

What underlies 'female protection'?

Are there converging mechanisms underlying sex differentiation, gender socialization, & the emergence of autism?

Caveats in current knowledge/literature:
- Many under-represented populations
- A lack of appreciation of multi-faceted sex and gender factors

Clinical implications

Status Quo: *Autism tends to be recognized/diagnosed later in females than in males (assigned sex at birth)*
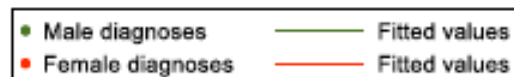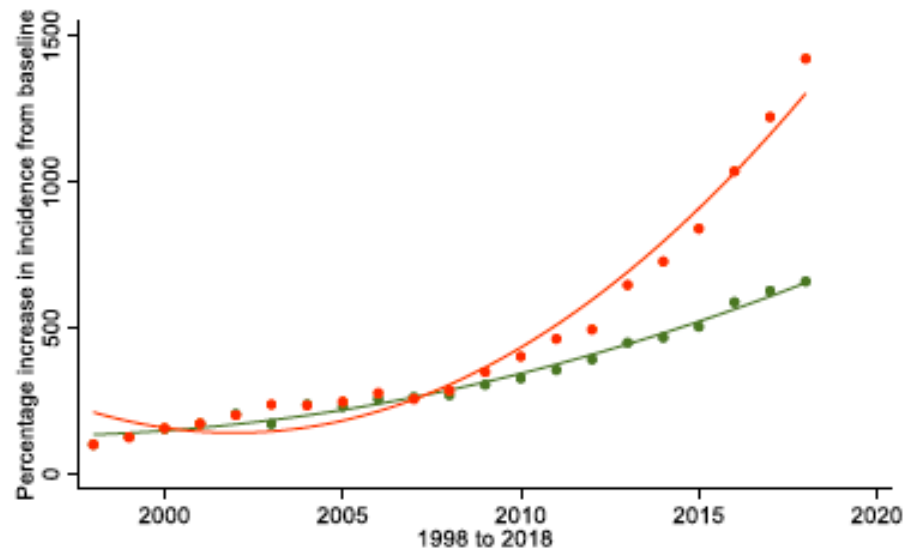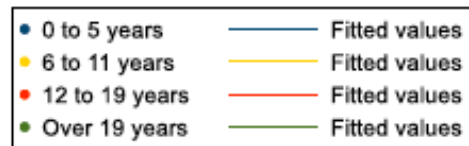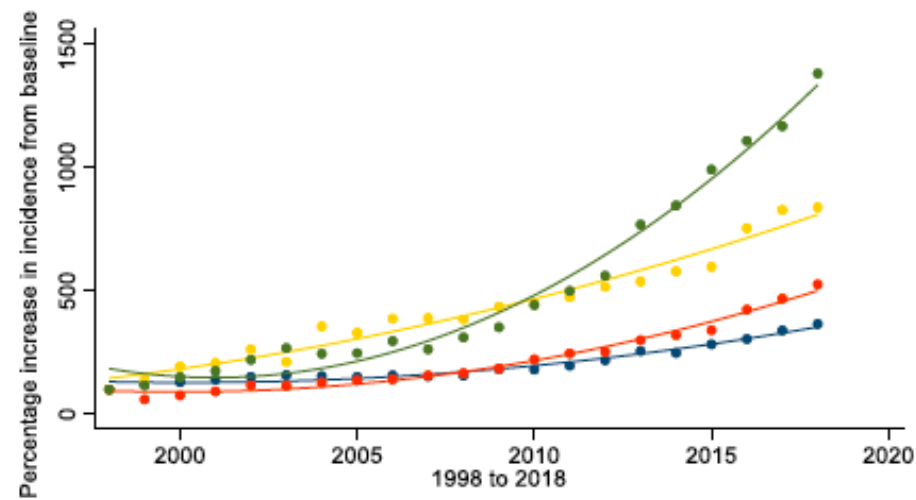
2002 US CDC autism surveillance data:

"The median age of identification for female subjects (6.1 years) was significantly older than that for male subjects (5.6 years)… Females in our sample were identified at a later age despite a tendency to be more cognitively impaired."

Shattuck et al., 2009, *JAACAP*

1998-2018 UK Clinical Practice Research Datalink (CPRD) primary care database:

"The mean age at which males received a diagnosis across the whole dataset was 12.3 years old (SD = 11.5) and for females 14.9 years old (SD = 12.4)."

Russell et al., 2021, *JCPP*

Factor 1 (contextual): *Expectancy bias, gender stereotypes, & diagnostic overshadowing may impede the recognition of autism in non-male individuals (assigned sex at birth)*

Level of Moderator (Sex)

Girls
b = 19.15
95% CI = [11.39, 26.91]

Boys
b = 10.25
95% CI = [6.8, 13.69]

Age of Diagnosis (AOD)

Verbal IQ

McDonnell et al., 2020, *JCCAP*; Also see Harrop et al., 2020, *Autism Res*
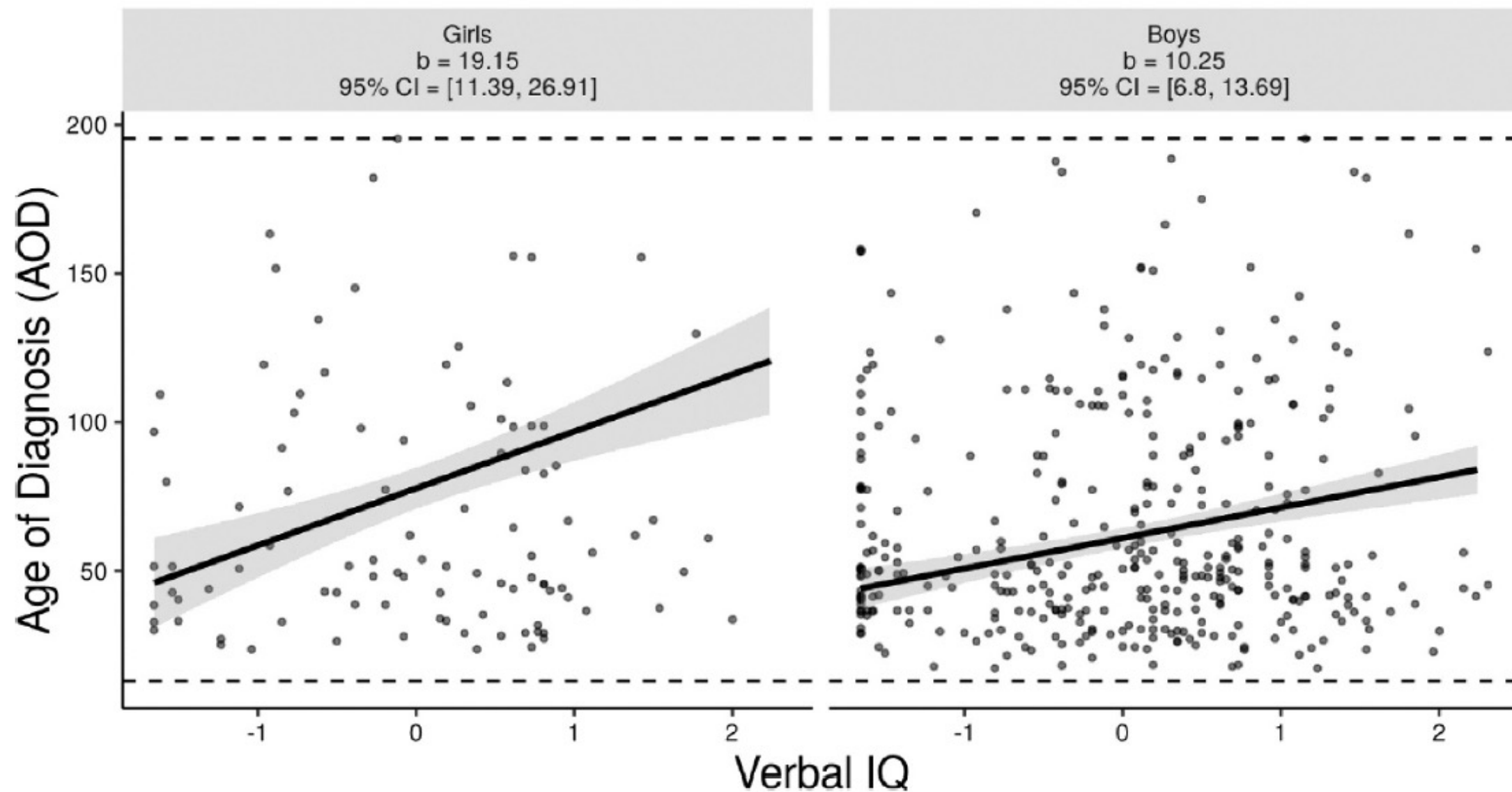
Autistic boys and girls (mean=10 years) *matched on ADOS scores*
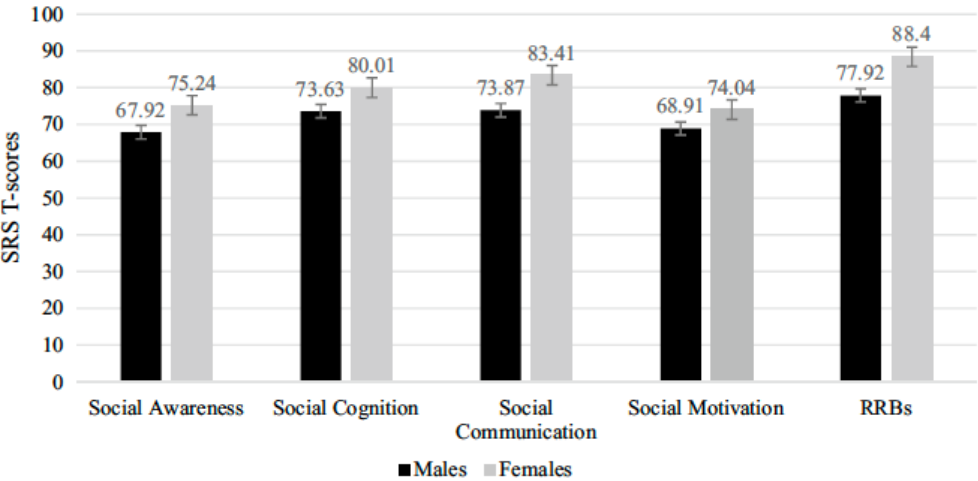
"…females who ultimately met criteria on gold-standard diagnostic measures were more severely affected in real-world settings than their male counterparts."

Ratto et al., 2018, *JADD*

Dworzynski et al., 2012, *JAACAP;* Duvekot et al., 2017, *Autism*
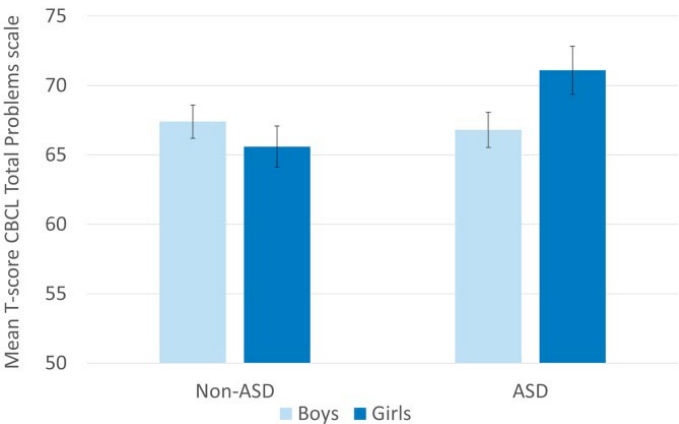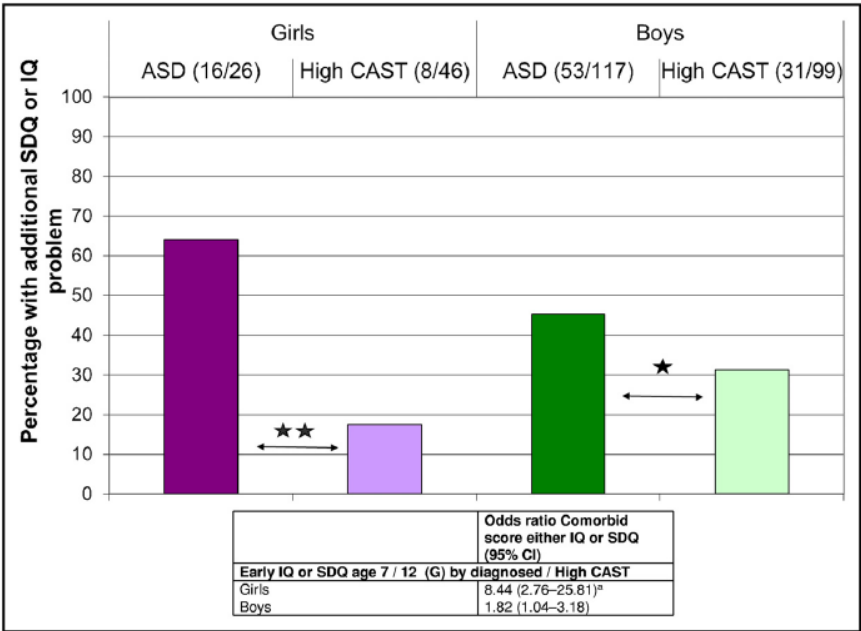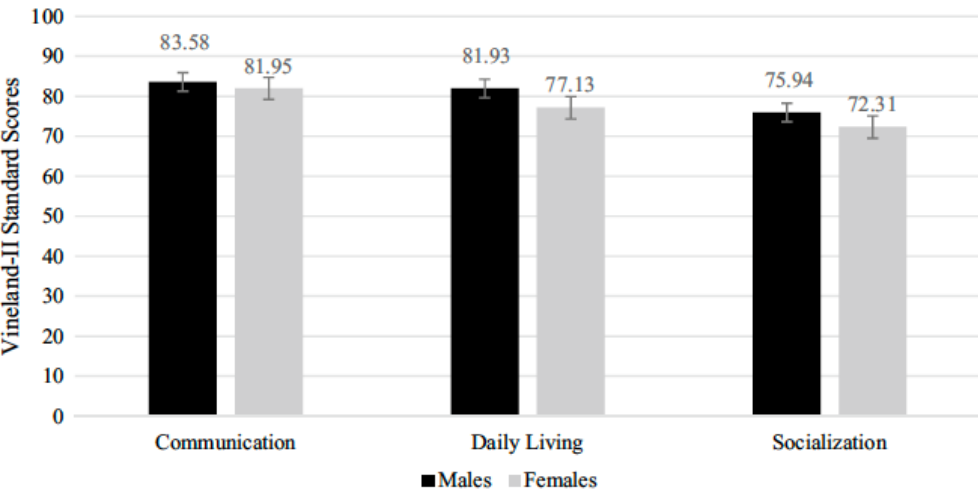
Netherlands Autism Register: N=1019 (494 M, 525 F), **>16 y/o**

Observed rates of prior diagnoses that were no longer present post-autism diagnosis for specific psychiatric conditions, and logistic regression parameters.

	Male		Female		Total		Logistic Regression				OR	Wald 95% CI	
	N	%	N	%	N	%	b	SE	Wald χ^2	p			
At least one prior diagnosis no longer present post-autism diagnosis	135	27.3	247	47	382	37.5	0.89	.17	42.23	<.001***	2.45	1.87	3.12
Personality Disorders	35	7.1	115	21.9	150	14.7	1.46	.21	46.75	<.001***	4.30	2.83	6.53
Mood Disorders	26	5.3	70	13.3	96	9.4	1.12	.25	20.53	<.001***	3.06	1.89	4.96
Anxiety Disorders	23	4.7	66	12.6	89	8.7	1.02	.26	16.04	<.001***	2.78	1.69	4.60
Burnout/Chronic Fatigue	11	2.2	41	7.8	52	5.1	1.61	.36	19.98	<.001***	5.00	2.47	10.13
Eating Disorders	3	0.6	26	5.0	29	2.8	2.18	.62	12.33	<.001***	8.85	2.62	29.91
Attention-Deficit/ Hyperactivity Disorder	15	3.0	24	4.6	39	3.8	.37	.34	1.13	.287	1.44	.74	2.82
Trauma-related Disorders	5	1.0	15	2.9	20	2.0	1.27	.54	5.54	.019	3.54	1.24	10.15
Oppositional Defiant Disorder/ Conduct Disorder	13	2.6	7	1.3	20	2.0	−.65	.49	1.81	.179	.52	.20	1.35
Substance Use Disorder	9	1.8	7	1.6	16	1.6	−.04	.53	.00	.947	.97	.34	2.72

"…the delay in receiving an autism diagnosis was 1.5 years in boys and 2.6 years in girls with pre-existing ADHD, compared with boys and girls without prior ADHD"

Kentrou et al, 2021, *Res Autism Spec Dis*; Kentrou et al., 2018, *Autism*

Danish National Patient Registry: N=2199 (1312 M, 887 F), **autism diagnosis in adulthood**
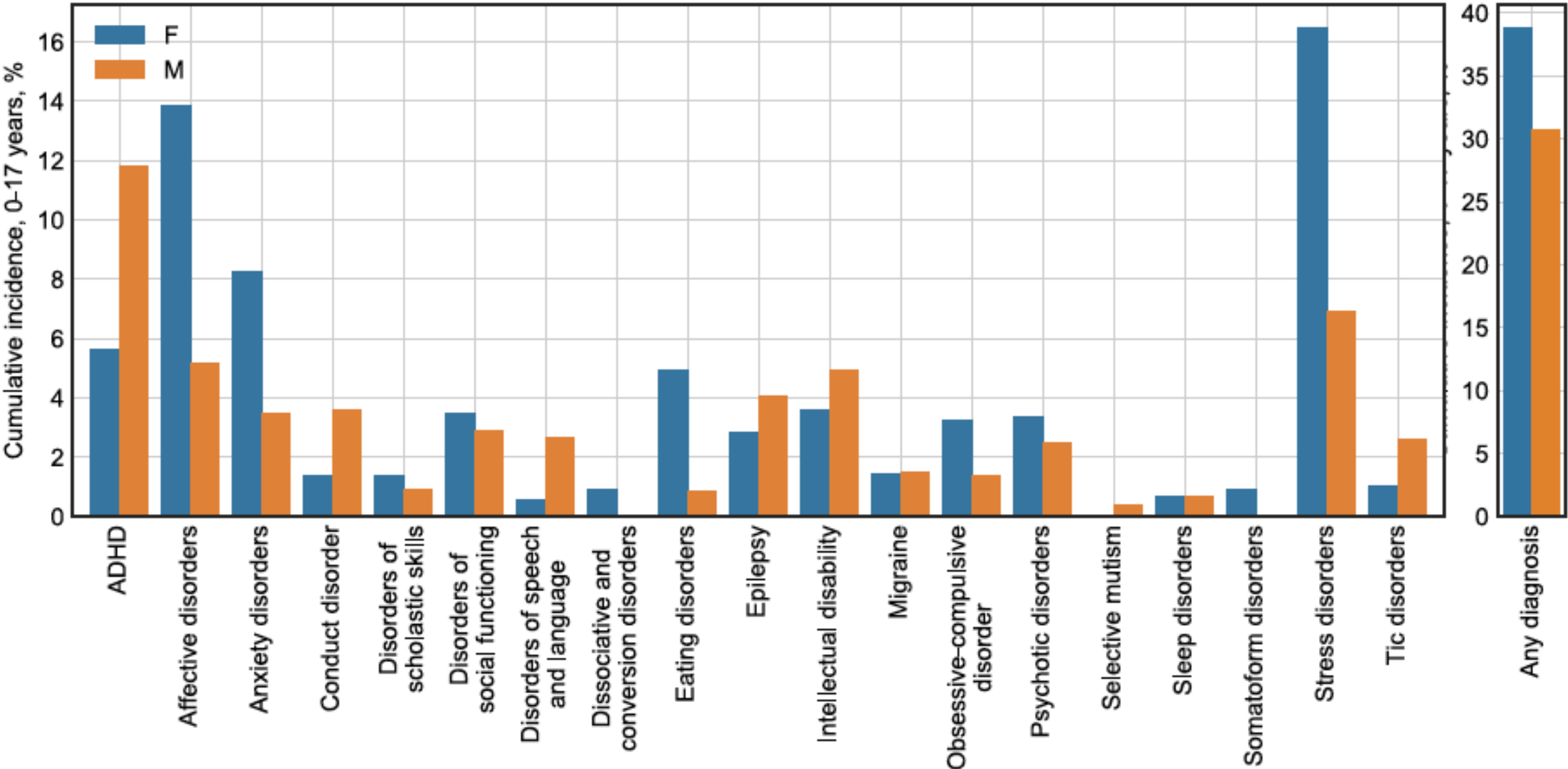
Recognition of Girls on the Autism Spectrum by Primary School Educators: An Experimental Study

Alana Whitlock, Kate Fulton, Meng-Chuan Lai ⓘ, Elizabeth Pellicano ⓘ, and William Mandy ⓘ

Vignette type	Word length	Core characteristic 1	Core characteristic 2	Core characteristic 3	Core characteristic 4
Female autism phenotype	180	Difficulty socializing, (higher friendship interest)▲	Restricted interest (social/animal focused)▲	Camouflage/ Mimicking▲	Autism-related emotional/ behavioral problem▲
		"best friends with another girl in the class, Mia, although Chloe does not seem to be friends with any of the other children"	"Chloe loves meerkats, and has pictures of them over her books, and will often reference them in her creative writing"	"Chloe will also copy a lot of Mia's behaviors"	"she is a fussy eater and will leave a fair amount of her food every lunchtime"
Male autism phenotype	195	Difficulty socializing	Restricted interest	Difficulty with change	Autism-related emotional/ behavioral problem
		"He tries to join in with the other children but tends to be ignored"	"if there is any free time in the classroom, Jack will spend it playing with his Harry Potter cards."	"He likes the routine of the classroom, but you have noticed that he can struggle moving from playtime back to the classroom"	"He has been involved in a couple of arguments and fights with his peers"

*"There was also an **interaction: female gender had an effect on ratings of the 'female phenotype', but not on the 'male phenotype' vignette**."*
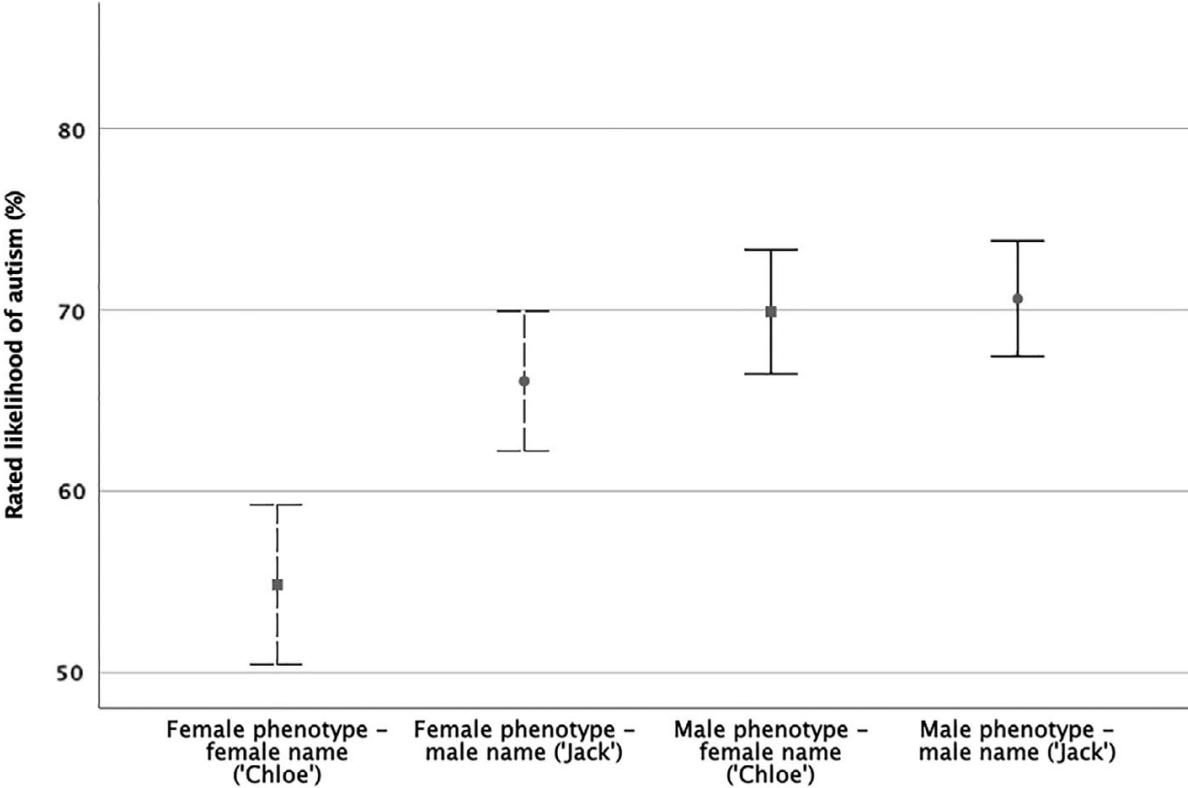
Factor 2 (individual): Sex- and gender-related factors can modulate autistic behavioural presentations and their developmental trajectories

Fewer RRBI on <u>conventional measures</u> in girls, and age-related differences

From a 27-site integrative analysis (N=8,985)

- *"**Boys received more severe RRB scores than girls** on both the ADOS and ADI-R (age 4+ algorithm)"*

- *"**Girls received more severe scores than boys on both SRS indices** [of social-communication and RRB], which **emerged in adolescence**"*

- *"Among children who ultimately receive a clinical ASD diagnosis, severity estimates do not systematically differ to such an extent that sex-specific scoring procedures would be necessary"*

- *"we could not address sex differences in phenotypic aspects **outside of these scores** [i.e. ADI-R, ADOS, SRS]"*

Example 1: Social attention & linguistic characteristics
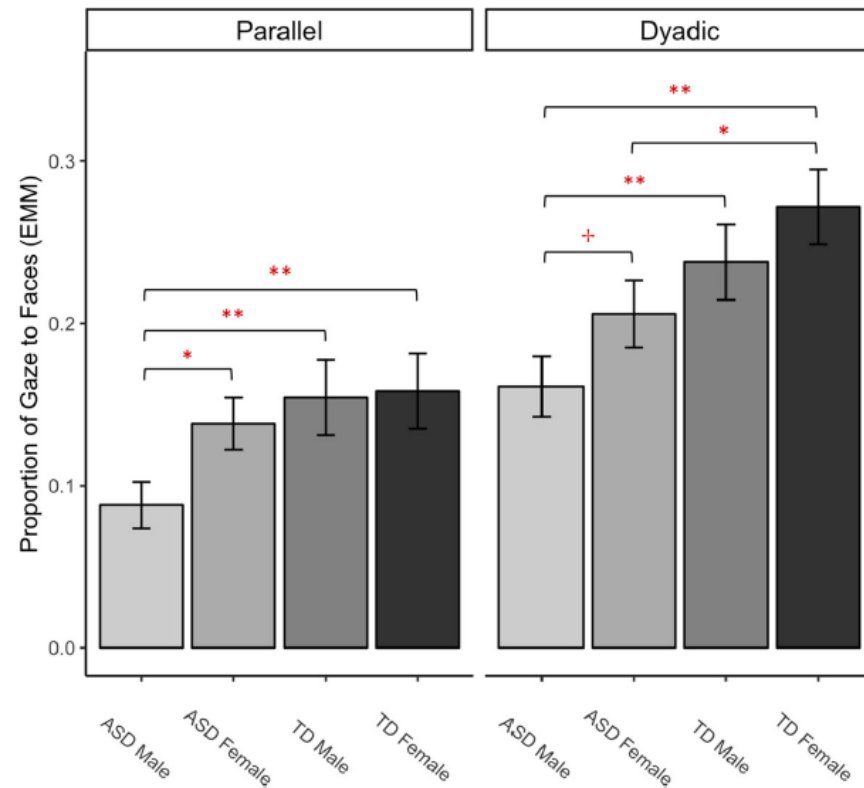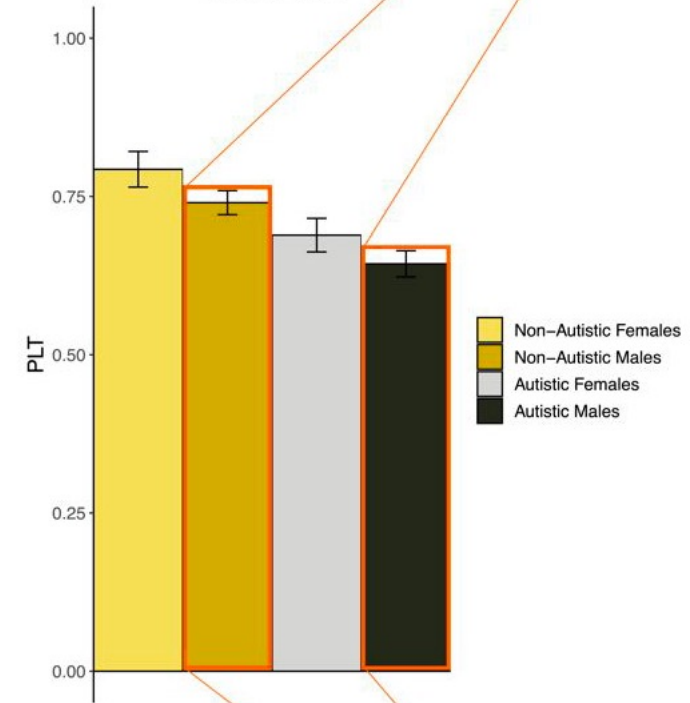
Natural language markers of social phenotype in girls with autism

Amber Song,[1] Meredith Cola,[2] Samantha Plate,[3] (iD) Victoria Petrulla,[2] Lisa Yankowitz,[2,4] Juhi Pandey,[2,5] Robert T. Schultz,[2,6] (iD) and Julia Parish-Morris[2,5] (iD)
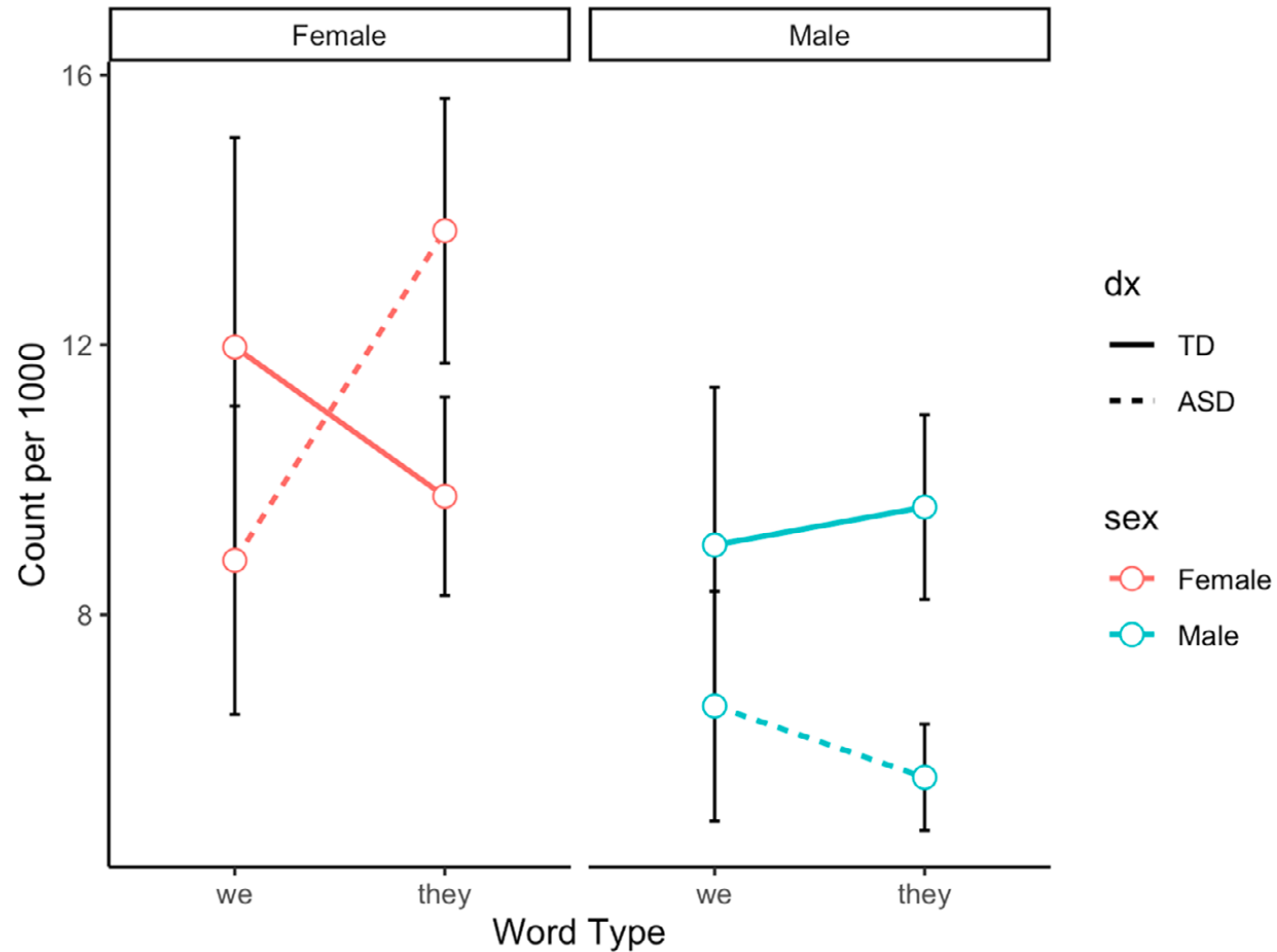
Example 2: Friendship and social motivation

Figure 1. Diagram showing the themes emerging from interviews with adolescent (a) girls and (b) boys. Bold lines denote themes unique to autistic participants and dashed lines denote themes unique to neurotypical participants. Bold text denotes the most common themes.
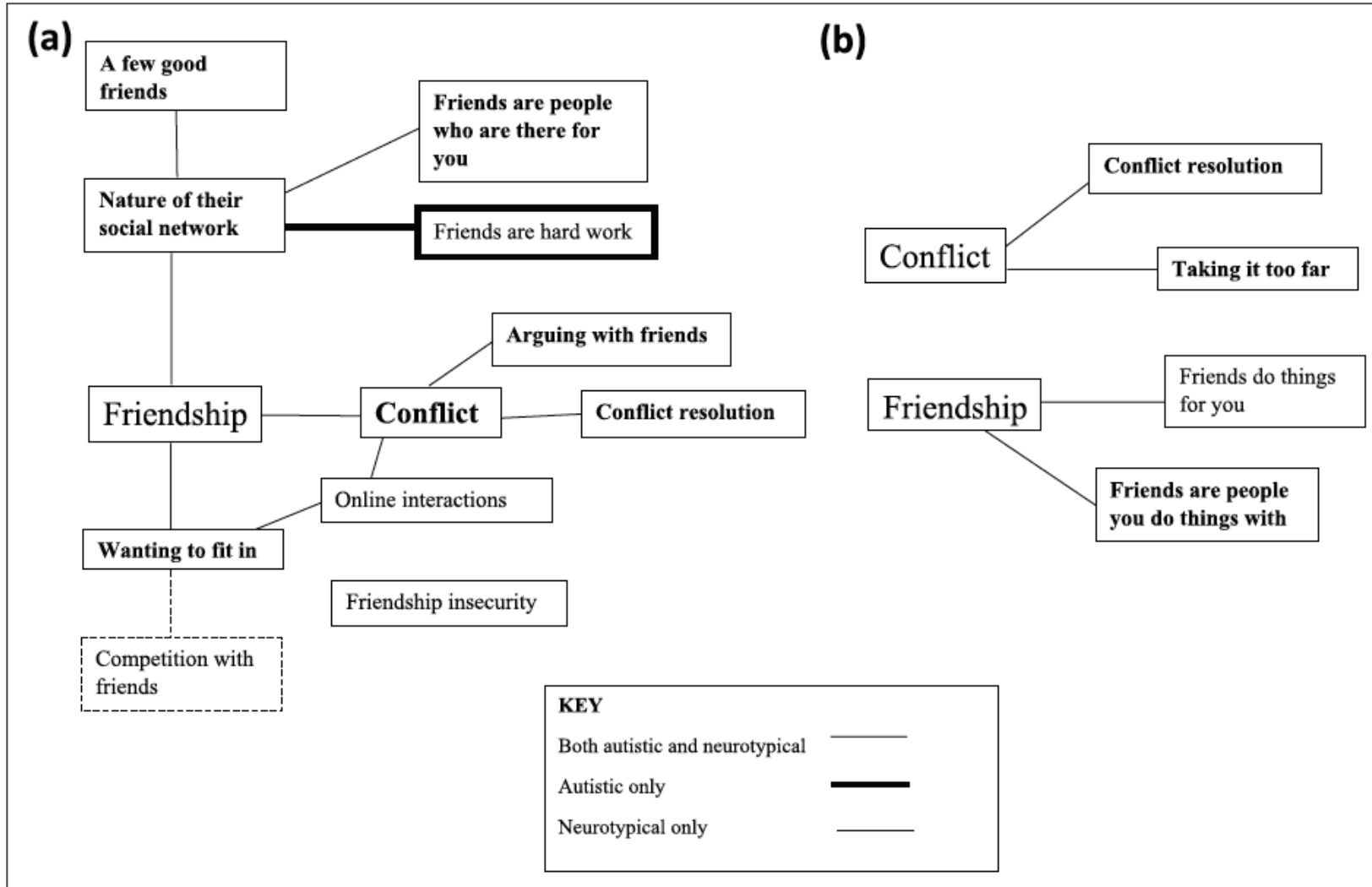
46 adolescents with special education needs, attending special schools in England

102 adolescents in the general community attending mainstream education

"...in many ways, **the friendships and social experiences of autistic girls are similar to those of neurotypical girls.**"

"**Autistic girls, however, have significantly more social challenges than their neurotypical peers,** experiencing more conflict and finding that conflict harder to manage successfully."

Example 3: (Social) developmental context and changes

ALSPAC (UK birth cohort): 9744 children in the general population; 4784 males and 4960 females
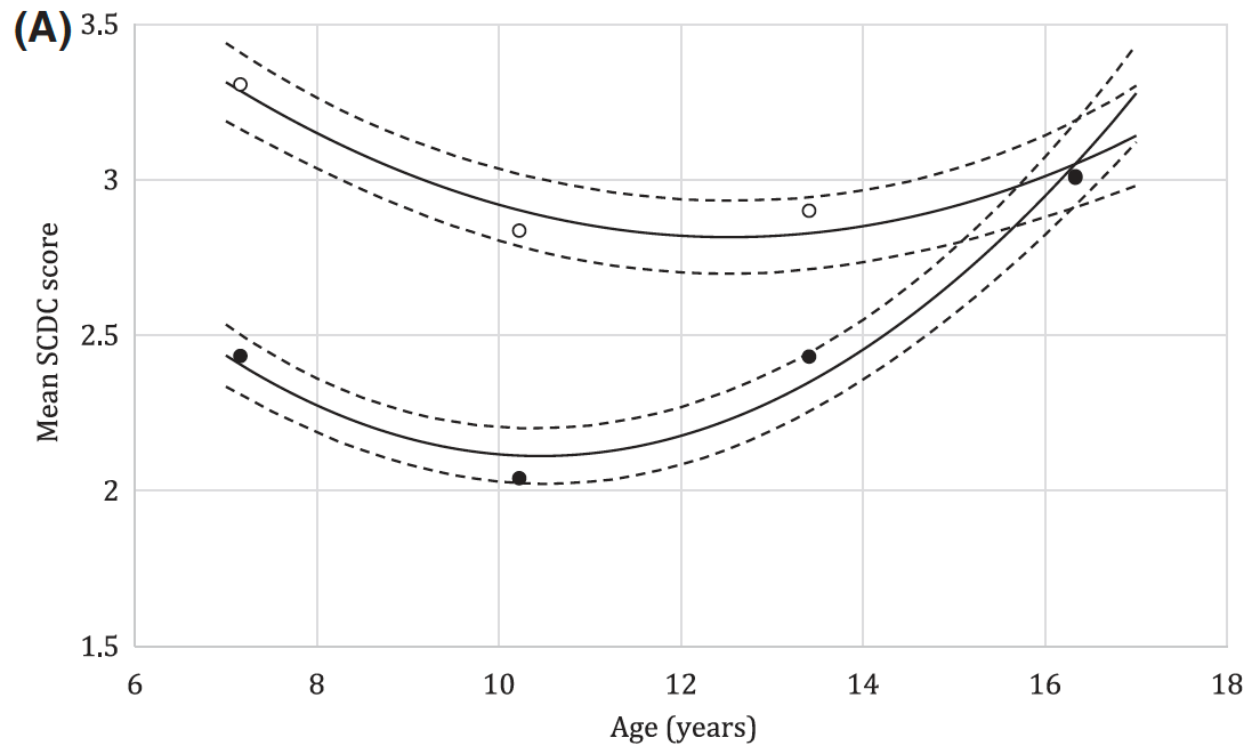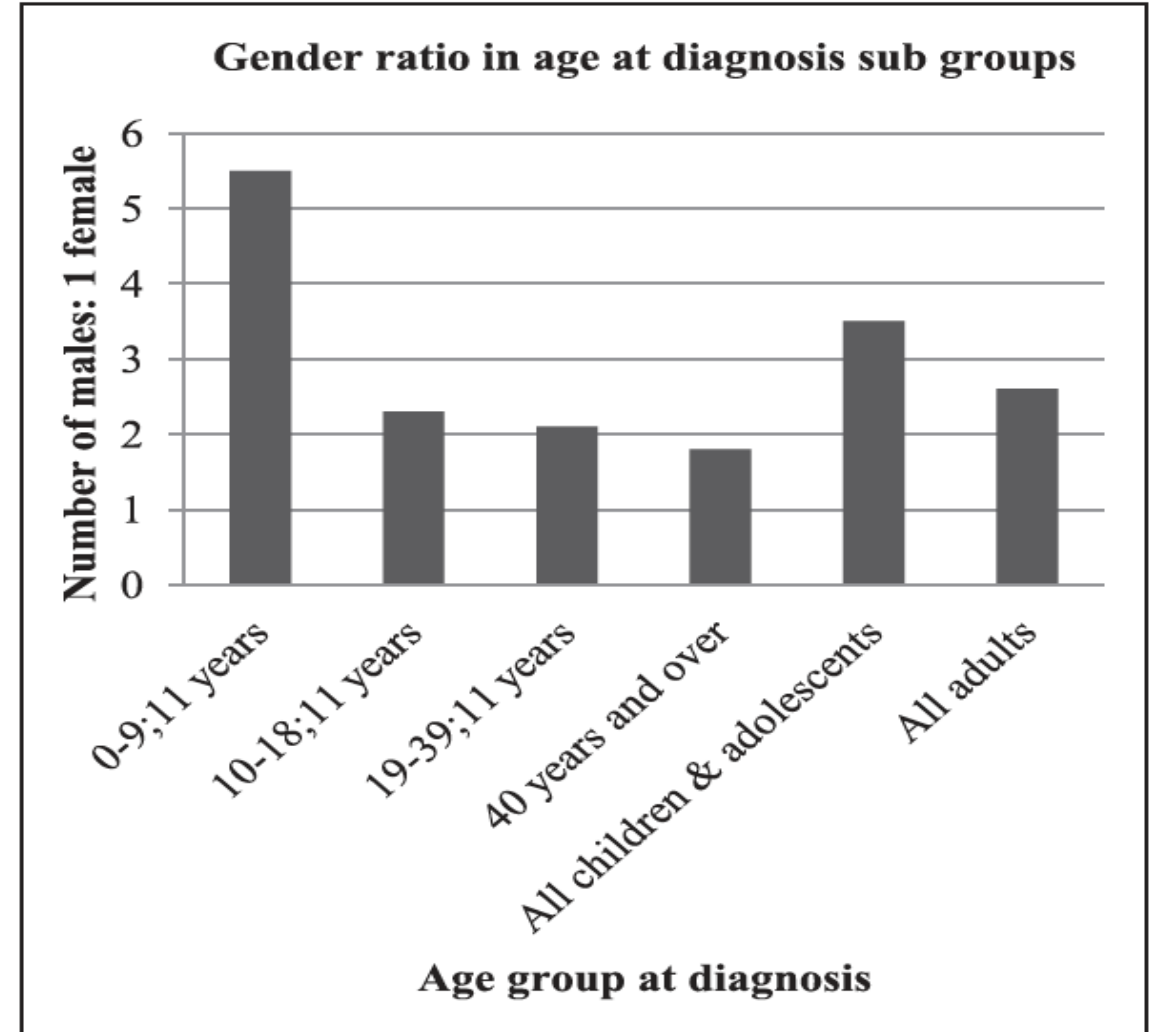
Baby Siblings Research Consortium: total 1824 infants; 193 autistic boys, 59 autistic girls
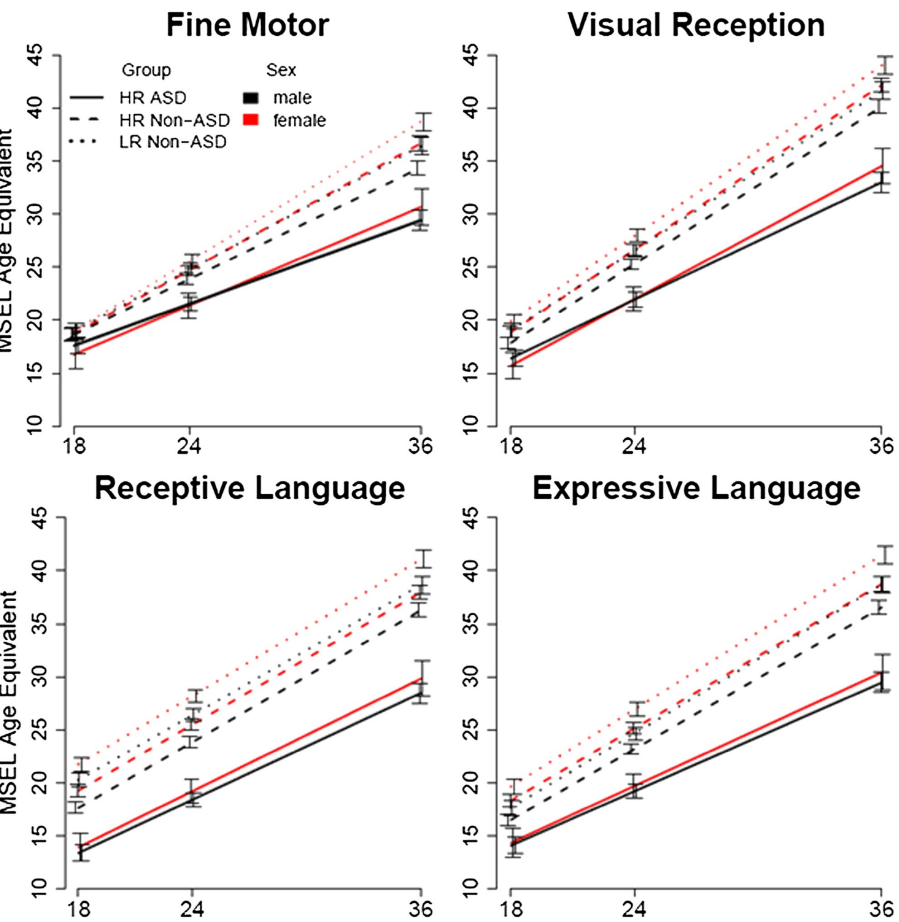
Pathways in ASD: 355 autistic boys, 66 autistic girls

Autism Phenome Project: 89 autistic boys, 36 autistic girls

Messinger et al., 2015, *Mol Autism*   Szatmari et al., 2015, *JAMA Psychiatry*   Waizbard-Bartov et al., 2021, *JADD*
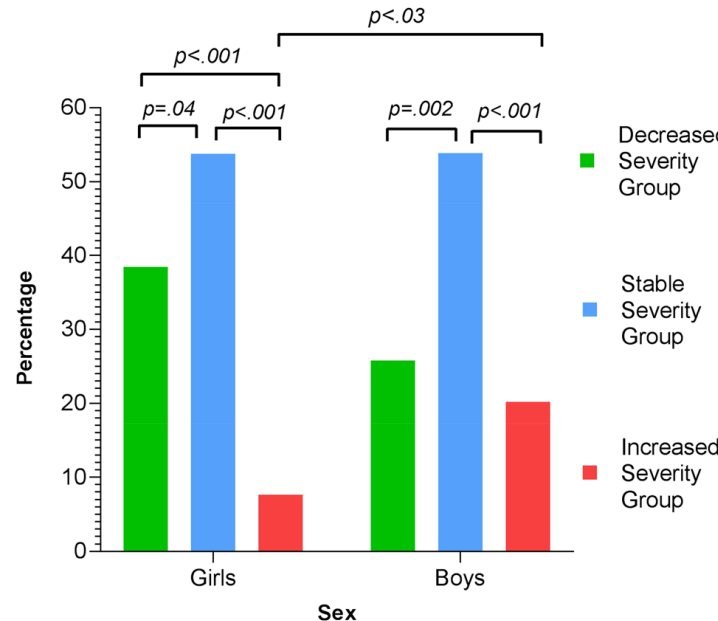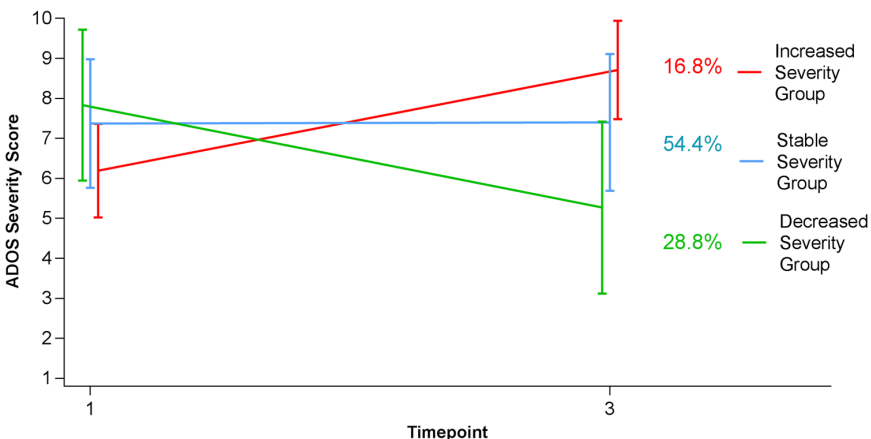
Example 4: Social coping ('masking', 'camouflaging', 'passing as non-autistic')

Compensation = finding ways around things that are naturally difficult

Example: Forcing yourself to make eye contact with someone

Masking = hiding parts of your autism

Example: Not talking about something you are really interested in

Assimilation = trying to fit in with everyone else so people don't notice you are different

Example: Talking to a stranger in a shop even if you don't want to

Development and Validation of the Camouflaging Autistic Traits Questionnaire (CAT-Q)

Laura Hull[1,6] · William Mandy[1] · Meng-Chuan Lai[2,3,4] · Simon Baron-Cohen[3] · Carrie Allison[3] · Paula Smith[3] · K. V. Petrides[5]

Cohen's *d* = 0.98
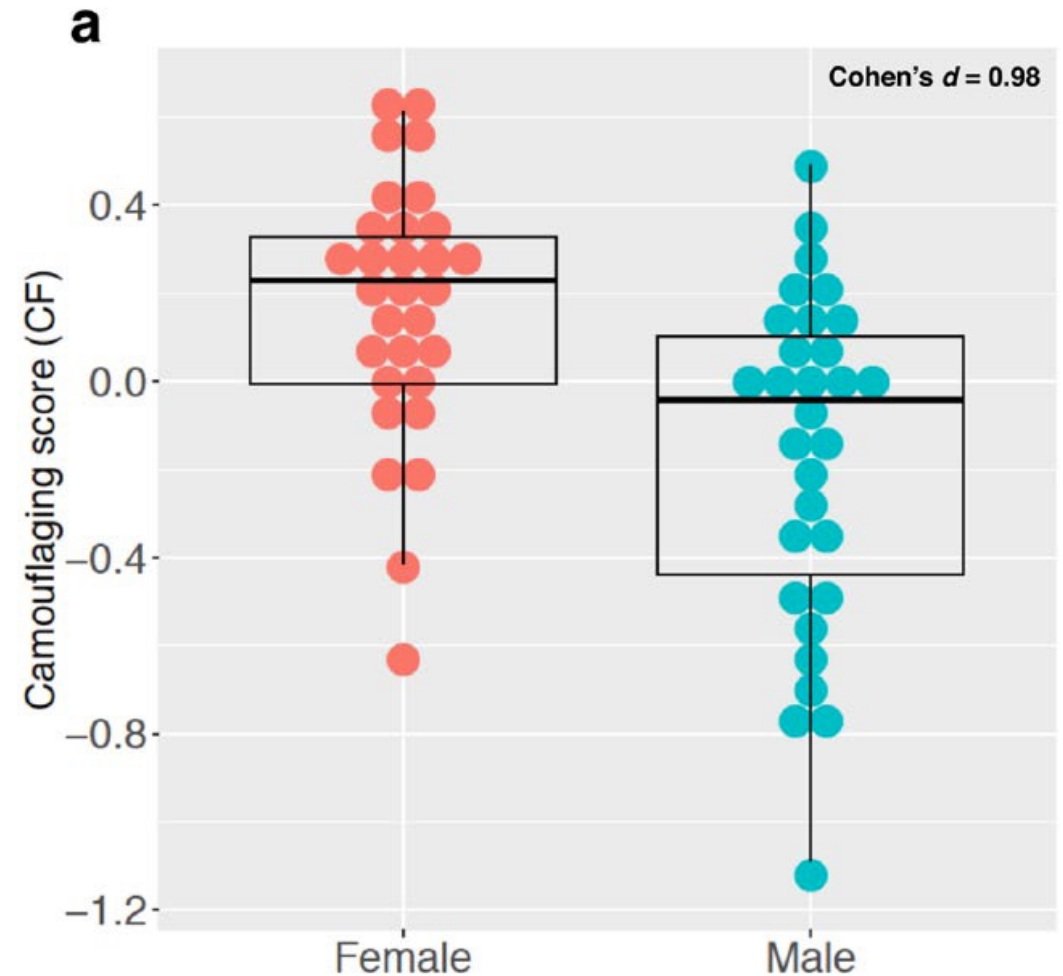
Playground behaviour

	TD boys	TD girls	ASD boys	ASD girls
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Games	41.50 (35.91)	13.75 (27.84)	10.87 (18.63)	6.68 (12.63)
Joint Engage	31.67 (31.44)	52.08 (35.01)	23.55 (27.80)	39.00 (31.46)
Solitary	3.81 (6.91)	7.92 (14.46)	43.57 (33.90)	26.69 (28.51)

Reciprocity in Interactive Drawing Test
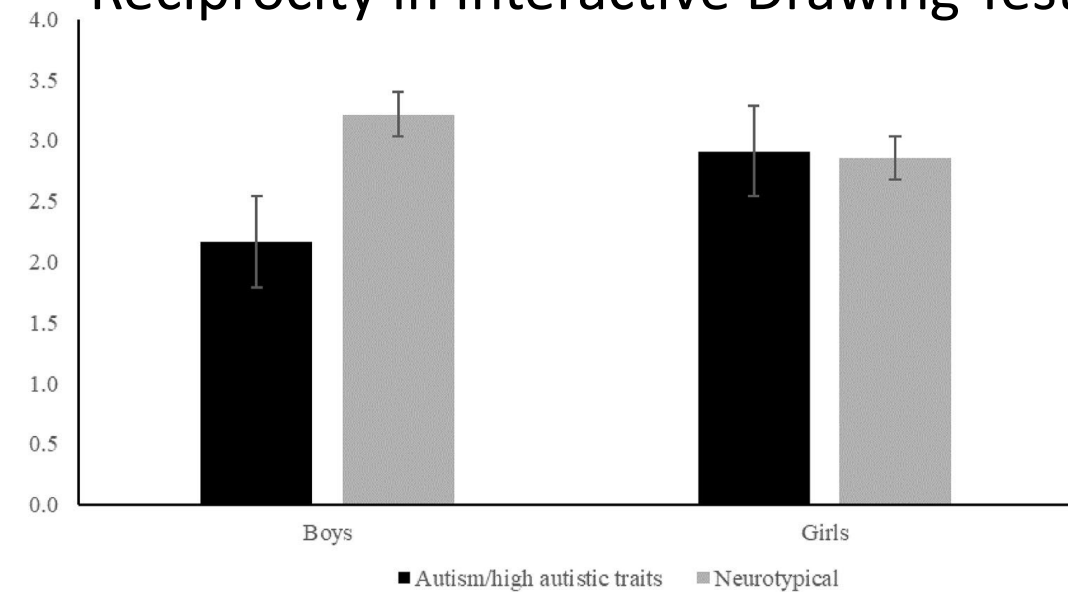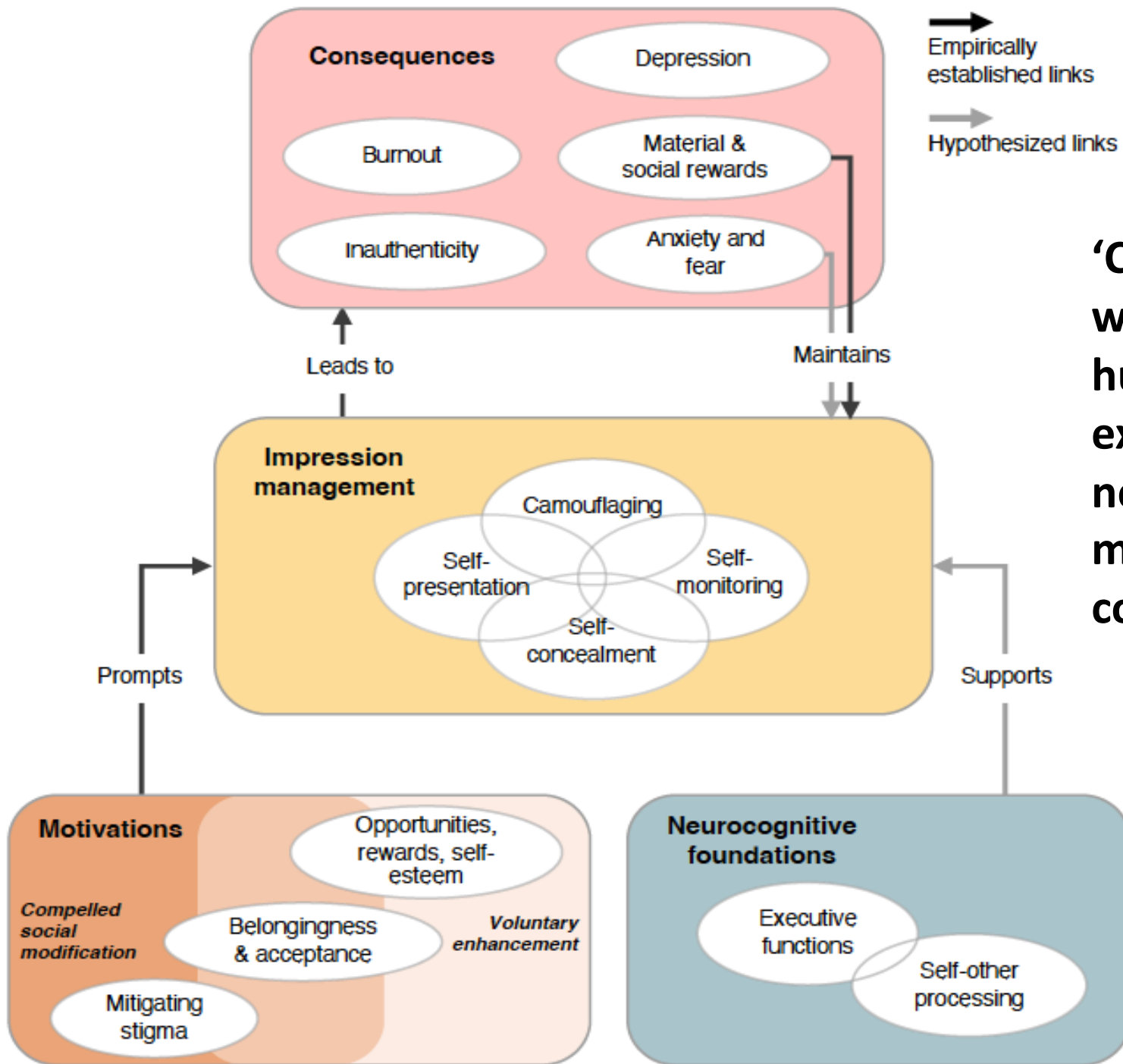
'Camouflaging' conceptually overlaps with impression management in humans in general, yet unique aspects exist considering autistic cognition in neurotypical contexts, across motivations, neurocognition, and consequences to wellbeing.

Health burden is high in autistic people, particularly in girls/women

	Number of datapoints in meta-analysis*	Autism population sample size (n)	Autism population		General population prevalence (95% CI or SE)	Subgroup moderator analysis				
			Pooled prevalence (95% CI; 95% PI)	I^2 (95% CI; p value†)		Prevalence in population or registry-based studies (95% CI; 95% PI)	Prevalence in clinical sample-based studies (95% CI; 95% PI)	R^2 (QE p value)	I^2 (95% CI)	QM p value
Attention-deficit hyperactivity disorder	89	210 249	28% (25–32; 4–63)	99·65% (99·55–99·85; <0·0001)	7·2% (6·7–7·8; point prevalence, aged ≤18 years)[46]	22% (17–26; 1–55)	34% (29–39; 7–69)	2·05% (<0·0001)	99·64% (99·60–99·84)	0·0004
Anxiety disorders	68	169 829	20% (17–23; 2–48)	99·53% (99·42–99·87; <0·0001)	7·3% (4·8–10·9; current prevalence, across ages)[47]	15% (11–19; 0·5–42)	26% (22–31; 1–56)	0% (<0·0001)	99·54% (99·20–99·85)	0·0002
Depressive disorders	65	162 671	11% (9–13; 0–33)	99·41% (99·39–99·81; <0·0001)	4·7% (4·4–5·0; point prevalence of MDD, across ages)[48]	8% (5–11; 0·01–28)	14% (11–18; 1–38)	0·23% (<0·0001)	99·40% (99·37–99·80)	0·0003
Bipolar and related disorders	38	153 192	5% (3–6; 0–19)	99·50% (99·40–99·82; <0·0001)	0·71% (0·56–0·86) for bipolar I; and 0·50% (0·35–0·64) for bipolar II (1-year prevalence, across ages)[49]	3% (2–5; 0–16)	7% (4–10; 0–24)	0·35% (<0·0001)	99·50% (99·48–99·81)	0·018
Schizophrenia spectrum and psychotic disorders	42	166 627	4% (3–5; 0–14)	99·18% (99·00–99·87; <0·0001)	0·46% (0·41–0·50; 1-year prevalence, across ages)[50]	2% (1–4; 0–11)	7% (4–9; 0–19)	0% (<0·0001)	99·18% (99·01–99·84)	0·0004
Obsessive-compulsive and related disorders	47	53 243	9% (7–10; 1–21)	96·85% (96·75–99·87; <0·0001)	0·7% (0·4–1·1; 1-year prevalence, aged ≥18 years)[51]	4% (2–6; 0–13)	12% (10–15; 3–26)	12·51% (<0·0001)	96·20% (96·17–99·37)	<0·0001
Disruptive, impulse-control, and conduct disorders	50	140 946	12% (10–15; 0–36)	99·52% (99·47–99·90; <0·0001)	8·9% (SE 0·5; 1-year prevalence, aged ≥18 years)[52]	7% (4–10; 0–28)	22% (17–27; 3–50)	0% (<0·0001)	99·53% (99·42–99·88)	<0·0001
Sleep–wake disorders	26	190 963	13% (9–17; 0–43)	99·87% (99·78–99·93; <0·0001)	3·7% (NA; 1-year prevalence, aged ≤18 years)[53]	11% (7–17; 0–39)	16% (8–25; 0–47)	8·52% (<0·0001)	99·85% (99·77–99·91)	0·356

Age effect: ADHD, depression, bipolar, SSD   **ID** effect: SSD

Sex/gender effect: depression

Human Development Index effect: OCD

Lai et al., 2019, *Lancet Psychiatry*

Physical health of autistic girls and women: a scoping review

Caroline Kassee[1,2†], Stephanie Babinski[2,3†], Ami Tint[1,4], Yona Lunsky[4,5], Hilary K. Brown[2,6], Stephanie H. Ameis[1,4,5,7], Peter Szatmari[1,5,7], Meng-Chuan Lai[1,4,5,7,8,9,10†‡] and Gillian Einstein[2,8,11,12†]

Kassee & Babinski et al., 2020, *Mol Autism*

AUTISTIC GIRLS & WOMEN

vs. AUTISTIC BOYS & MEN

HIGHER OVERALL PHYSICAL HEALTH CHALLENGES

HIGHER PREVALENCE OF EPILEPSY
7.0% of autistic girls/women
3.9% of autistic boys/men
(0.73% of general population boys/men)

vs. NON-AUTISTIC GIRLS & WOMEN

HIGHER OVERALL PHYSICAL HEALTH CHALLENGES

HIGHER PREVALENCE OF EPILEPSY
7.0% of autistic girls/women
0.69% of general population girls/women

HIGHER PREVALENCE OF ENDOCRINE AND REPRODUCTIVE HEALTH ISSUES, e.g. PCOS
7.8% of autistic girls/women
3.5% of general population girls/women

Key Practical Implications

- *Clinicians need to regularly monitor and address physical health care needs for autistic people, especially female individuals.*
- *Particular attention should be paid to the risks of epilepsy, endocrine and reproductive health issues, and other neurological, gastrointestinal, metabolic, nutritional, and immune conditions.*
- *Developing a women's health lens when providing clinical care to autistic girls/women is essential.*

Neurodiversity intersects with gender and sexual diversity

? UNCLEAR MECHANISTIC LINKS

Autism, neurodevelopmental conditions, and **gender diversity**

675 adolescents (age >15) and adults registered in the Netherlands Autism Register (NAR)

Table 2 Assigned gender at birth and gender identity

Assigned gender at birth	Male n (%)	Female n (%)
Feels male	299 (91.7)	3 (0.9)
Partly male, partly female	10 (3.1)	31 (8.9)
Not male, nor female	2 (0.6)	26 (7.4)
don't know (yet)	4 (1.2)	9 (2.6)
Different (e.g. human, no sex)	8 (2.5)	8 (2.3)
Feels female	3 (0.9)	272 (77.9)

n (%)	Men		Women	
	ASD (n=316)	TD (n=3927)	ASD (n=343)	TD (n=4137)
Feels attracted to				
Men only	16 (5.1)	150 (3.8)	194 (56.6)**a	3601 (87)
Both men and women	27 (8.5)	184 (4.7)	77 (22.4)	418 (10.1)
Women only	258 (81.6)**a	3549 (90.4)	21 (6.1)	53 (1.3)
None of these	15 (4.7)	44 (1.1)	51 (14.9)	65 (1.6)
In a relationship	158 (50)**	2916 (74.3)	162 (47.2)**	2923 (70.7)
With a man	8 (5.1)	113 (3.9)	151 (93.2)	2861 (97.9)
With a woman	150 (94.9)	2803 (96.1)	11 (6.8)*	62 (2.1)
Living together with partner	136 (86.1)	2450 (84)	130 (80.2)	2324 (79.5)

Dewinter et al., 2017, *JADD*

Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals

Varun Warrier [1], David M. Greenberg[1,2], Elizabeth Weir [1], Clara Buckingham[1], Paula Smith[1], Meng-Chuan Lai [1,3,4], Carrie Allison[1] & Simon Baron-Cohen[1]
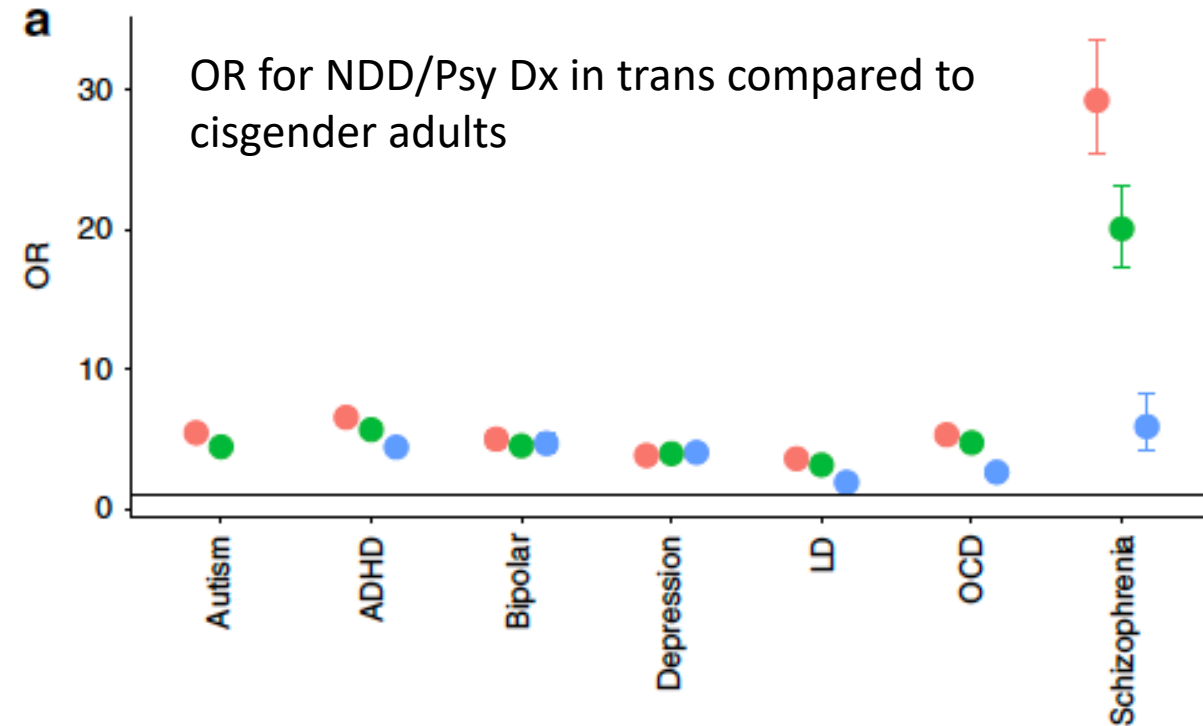
a

OR for NDD/Psy Dx in trans compared to cisgender adults

Warrier et al., 2020, *Nature Comm*

Biological heterogeneity implications

The common (neuroimaging) approach:
'where', then 'how it relates to behaviour'

Localization: Where in the brain the features of autism are different between sexes (i.e. sex-dependent)

- Examining **diagnosis-by-sex interactions** using mass-univariate regression models
- Examining **diagnosis effects stratified by sex**

Inferring function based on the brain region

Example 1: Intrinsic functional organization

rs-fMRI data from **13 sites** (ABIDE I+II), **7-18 years**
444 autism: 362 male, **82 female**
575 control: 409 male, 166 female

Floris, Filho et al., 2021, *Mol Autism*
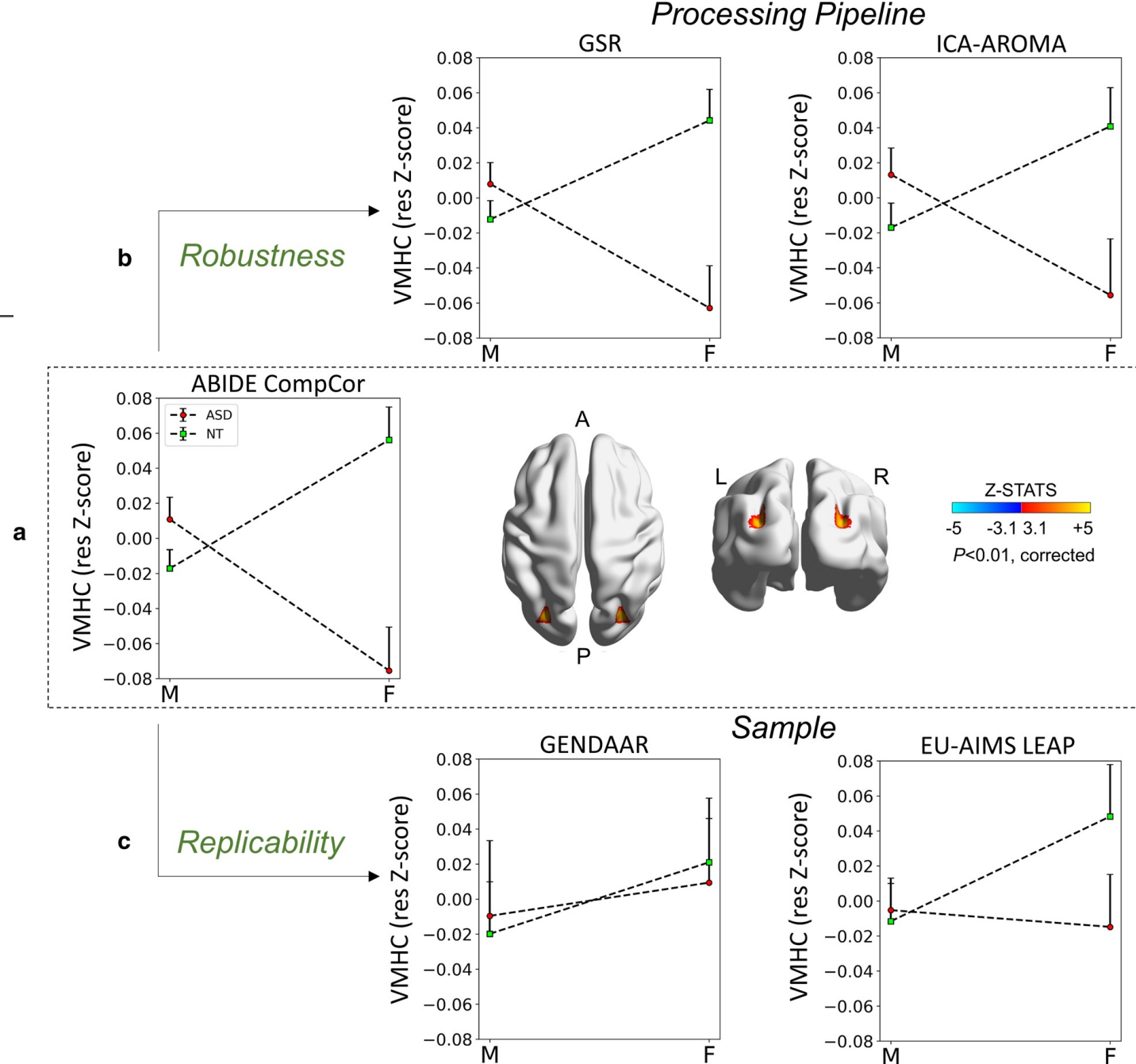
a Overlap of VMHC cluster with cognitive ontology maps
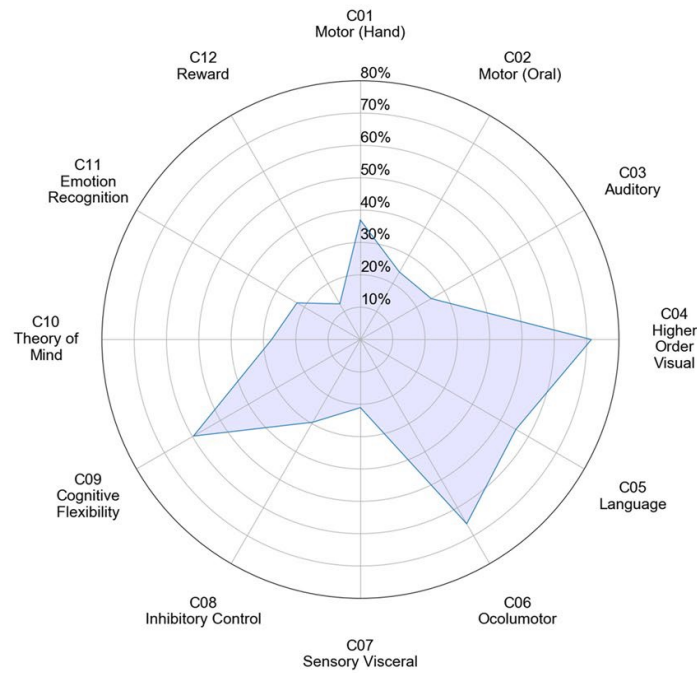
b Neurosynth terms correlation with VMHC cluster
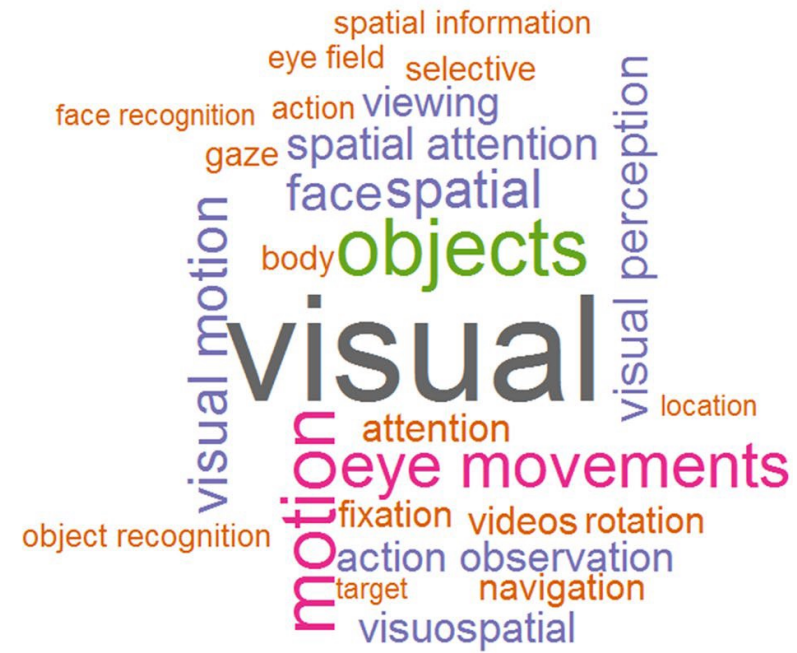
c Correlation between social-affect ADOS scores and VMHC cluster
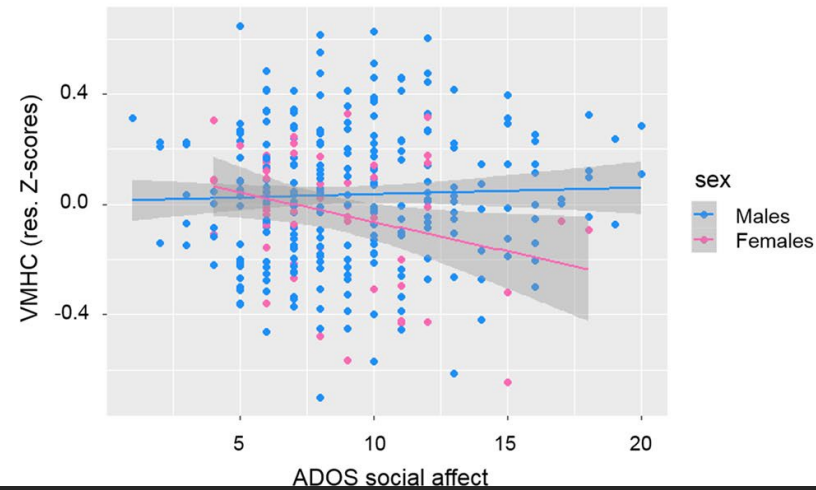
Example 2: Morphometry

T1w sMRI data from **12 sites**, **2-65 years**
491 autism: 362 male, **129 female**
836 control: 481 male, 355 female
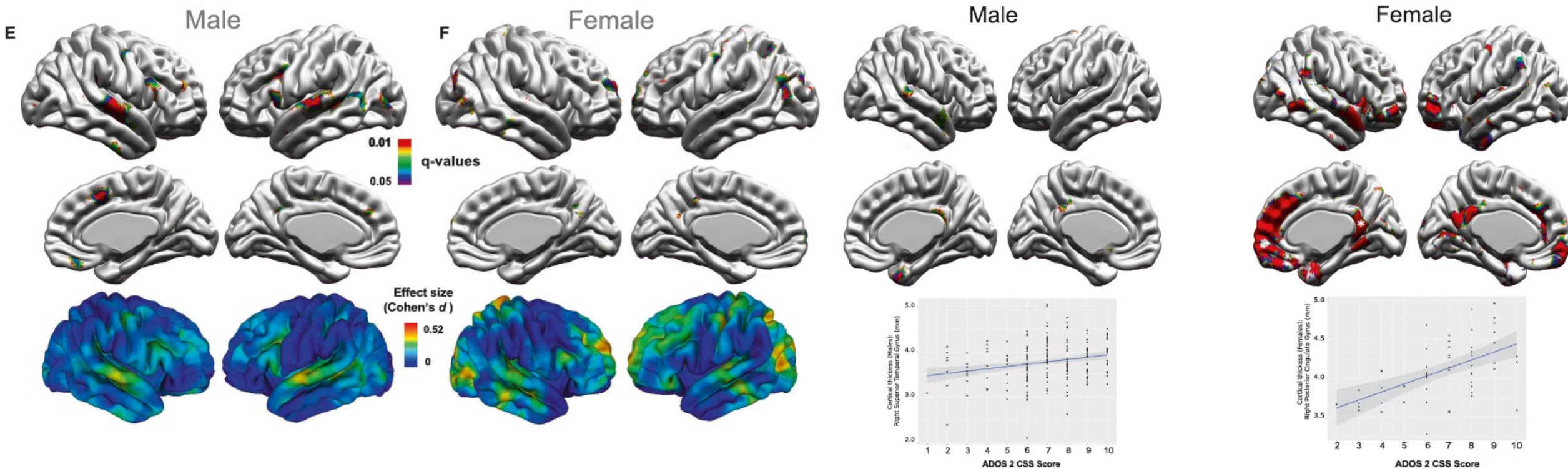
A new 'global' approach

Whole-brain pattern: How is the overall brain features of autism modulated by sex?

○ Global pattern ←→ fundamental 'global' mechanisms

○ 'Quantitative' sex-modulation

○ 'Qualitative' sex-modulation

Ronald et al., 2006, *JAACAP*
Ronald et al., 2011, *Mol Psychiatry*
Lai et al., 2017, *J Neurosci Res*

Behavioural Genetics
quantitative sex differences — degree of genetic/environment influences on autism that vary between males and females
qualitative sex differences — different genetic/environmental influences of autism affecting males and females

Human Neuroimaging
quantitative sex-modulation — same brain involvement, with larger-effect changes in autistic females than in males
qualitative sex-modulation — different brain involvement, with different changes in autistic females than in males

A simple univariate example
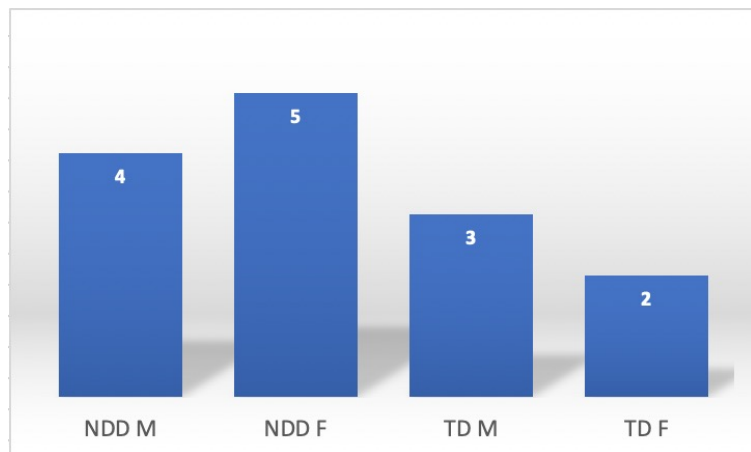
Quantitative sex-modulation
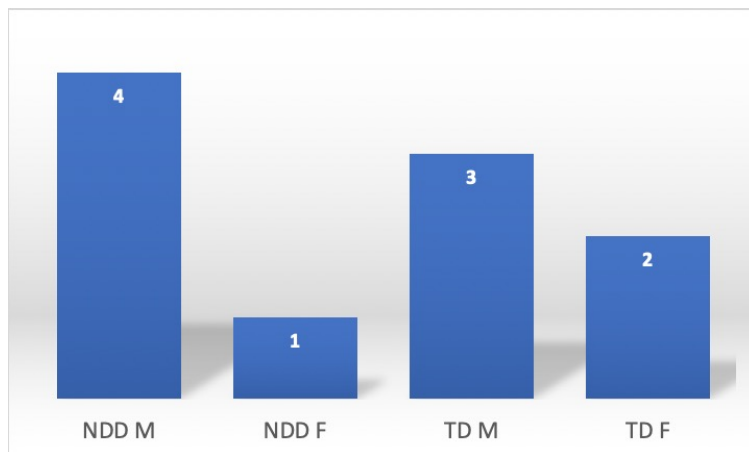
Qualitative sex-modulation

T1w sMRI data from 1 site (with **2 scanner versions**), **3-50 years**
373 (569 scans) ASD: 299 (467 scans) male, **74 (102 scans) female**
466 (614 scans) control: 240 (334 scans) male, 226 (280 scans) female

A

local magnitude model

B
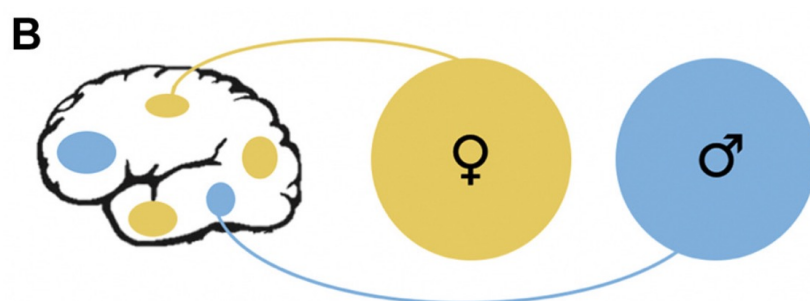
spatial dissimilarity model

Hammill et al., 2021, *Biol Psychiatry: CNNI*
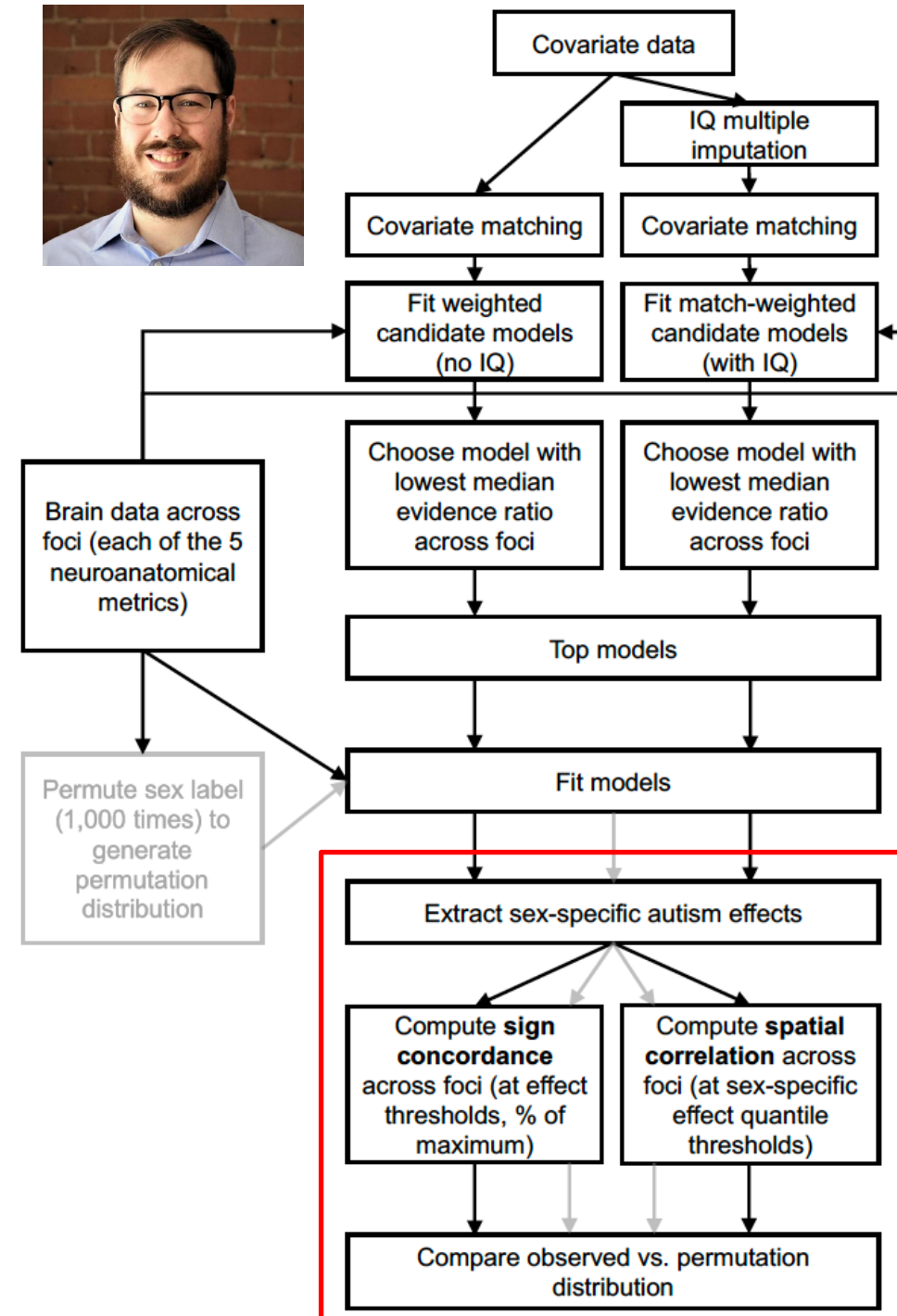
No evidence supporting the *quantitative sex-modulation model*
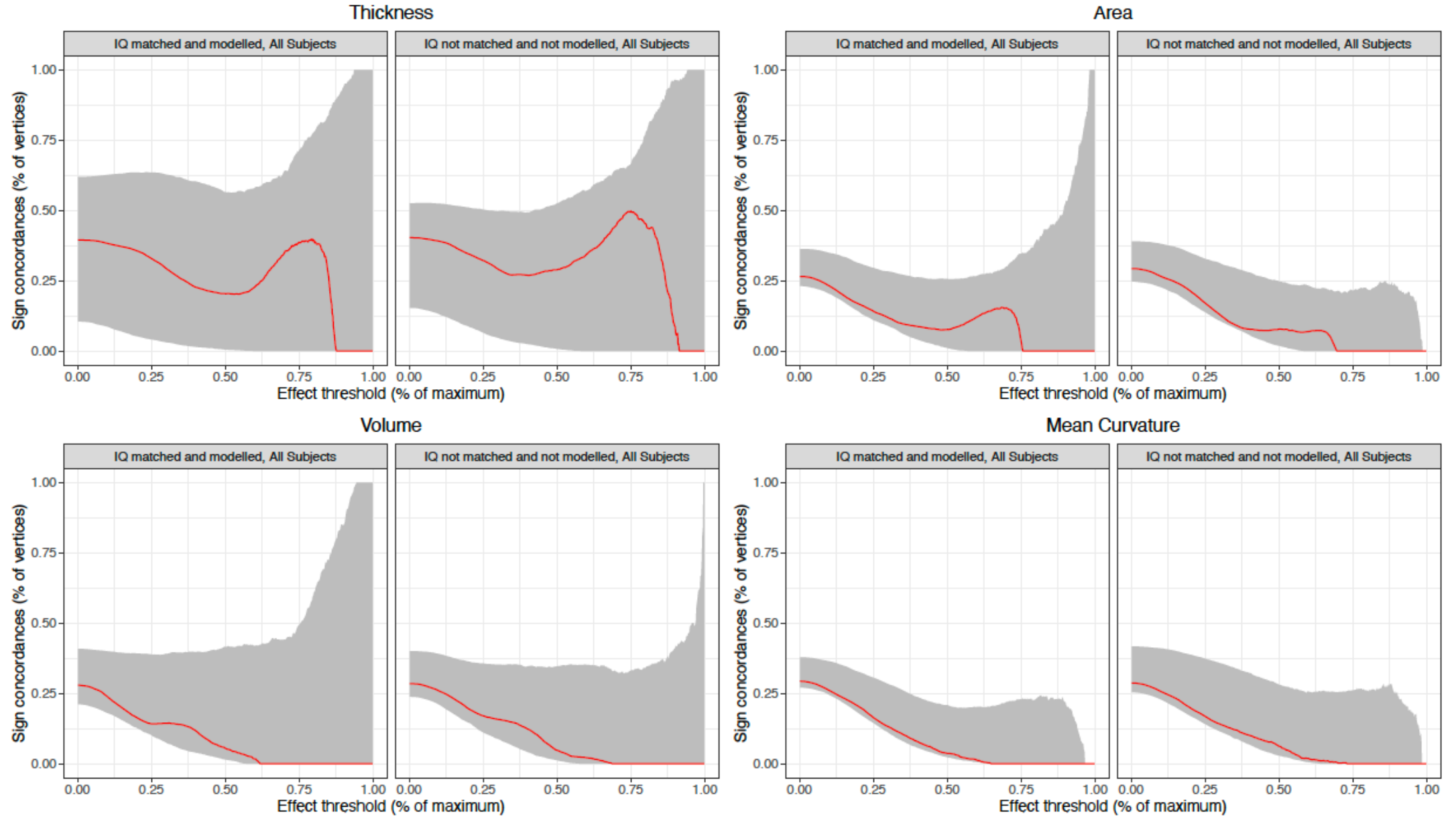
Indicators supporting the *qualitative sex-modulation model* on cortical mean absolute curvature and subcortical volume, but not other metrics

Hammill et al., 2021, *Biol Psychiatry: CNNI*
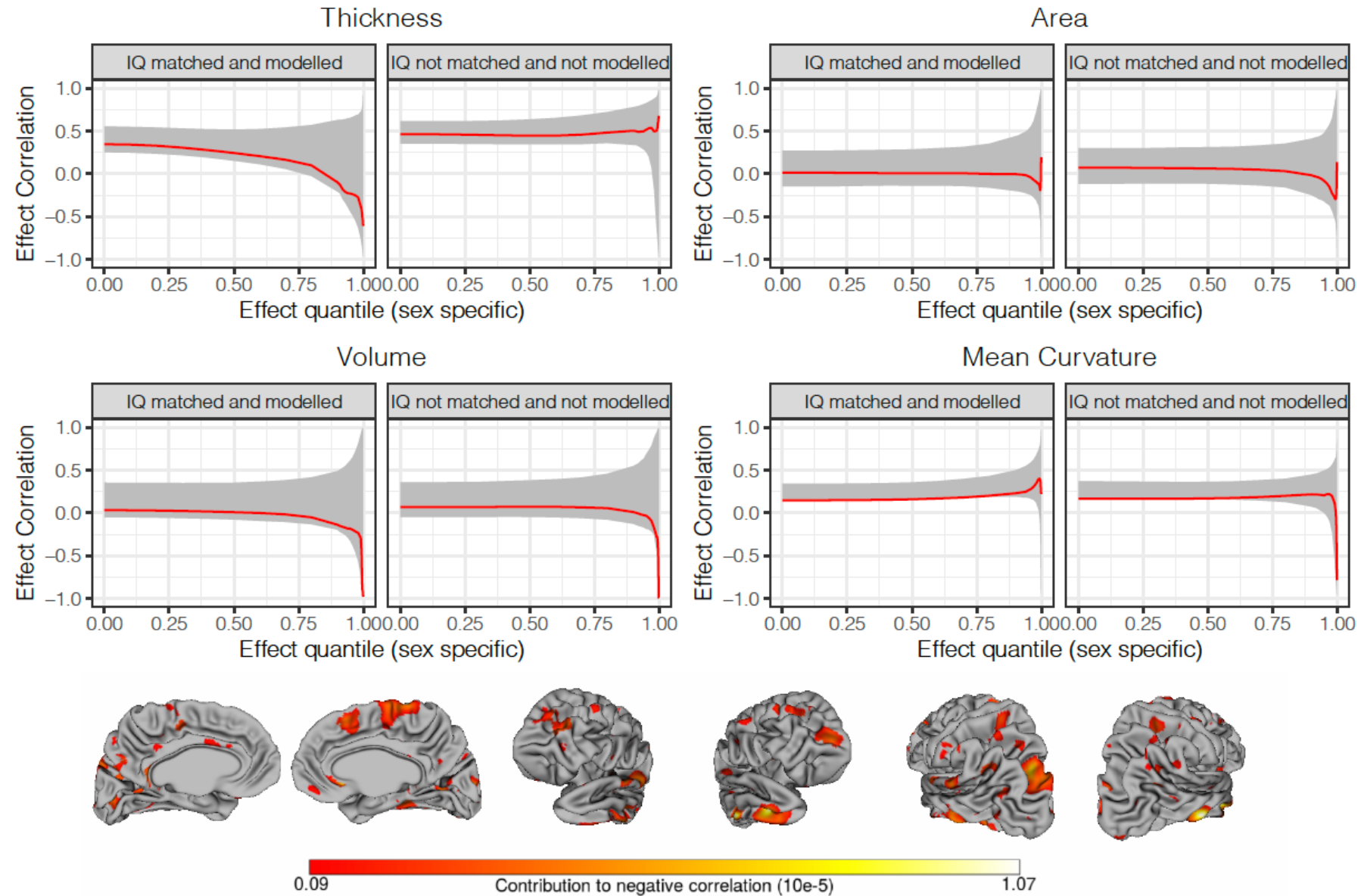
Aetiological implications

The so-called 'female protection' in autism aetiology applies not only to rare, but also common, genetic variants

? ACTUAL MECHANISMS OF SO-CALLED 'PROTECTION' ARE STILL UNCLEAR

? GENETIC – NEURODEVELOPMENT – NEUROPHENOTYPE – BEHAVIOUR PATHWAYS

SPARK & SSC

REACH, SPARK & SSC

Wigdor et al., 2021, *medRxiv*; Antaki et al., 2021, *medRxiv*

Satterstrom et al., 2020, *Cell*
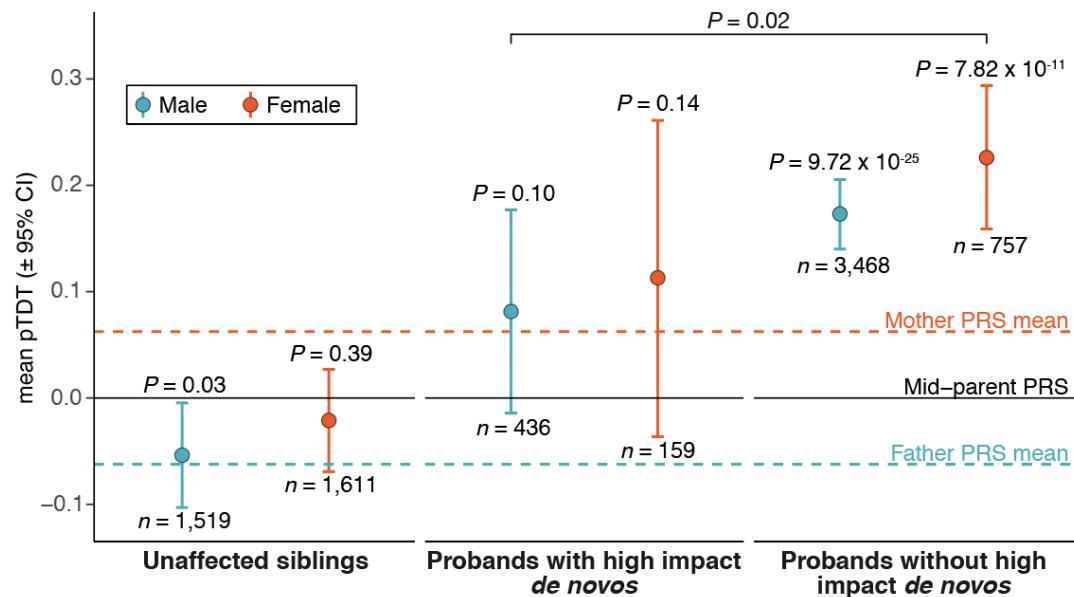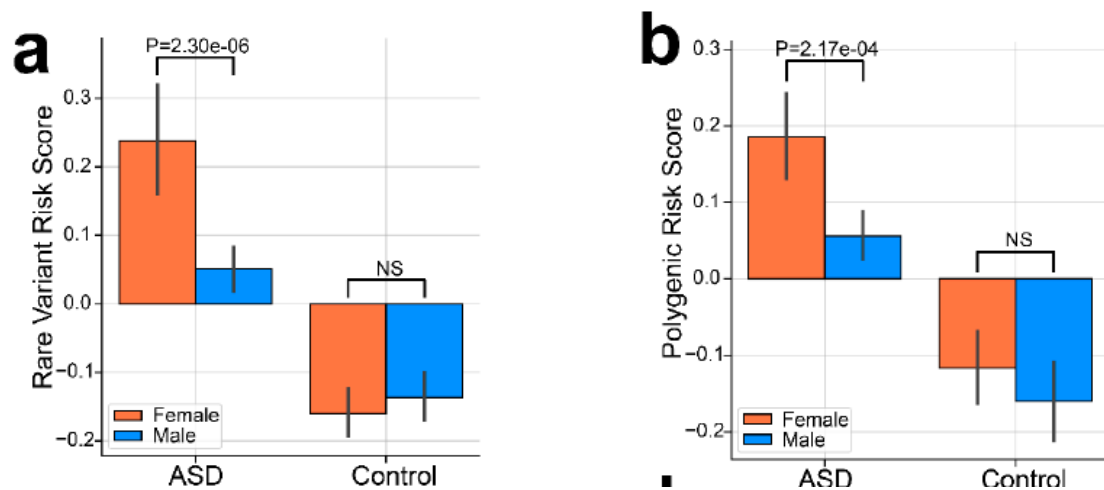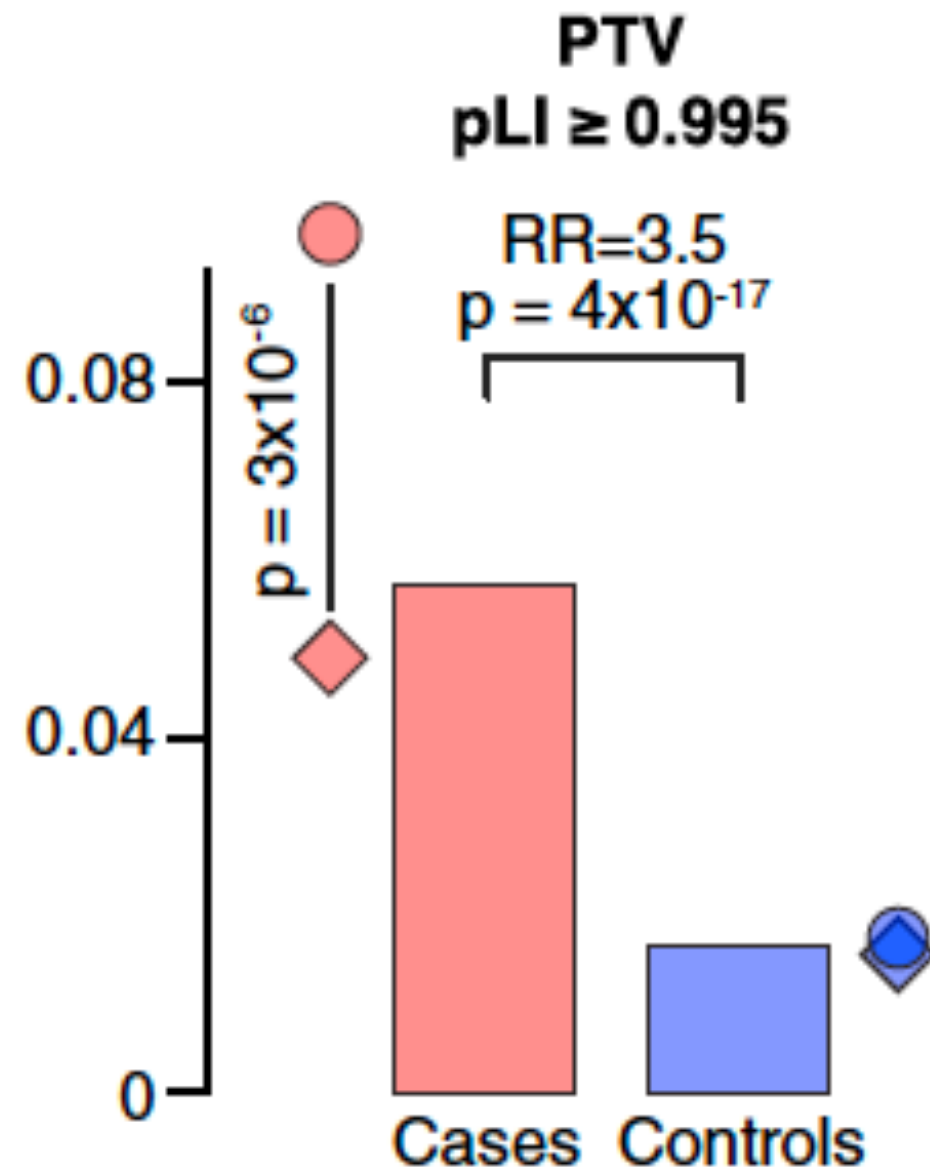
SPARK and SSC
 -- stratified by IQ level

Warrier et al., 2021, *medRxiv*
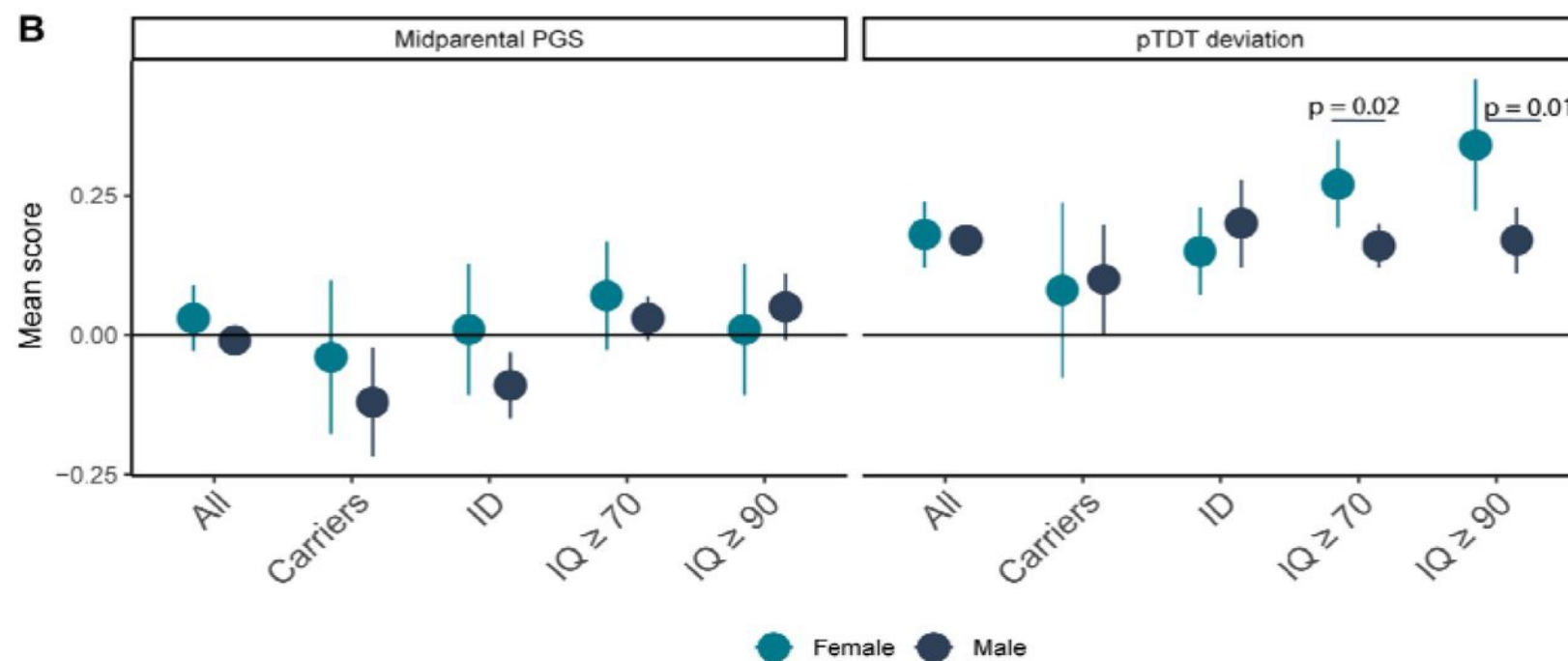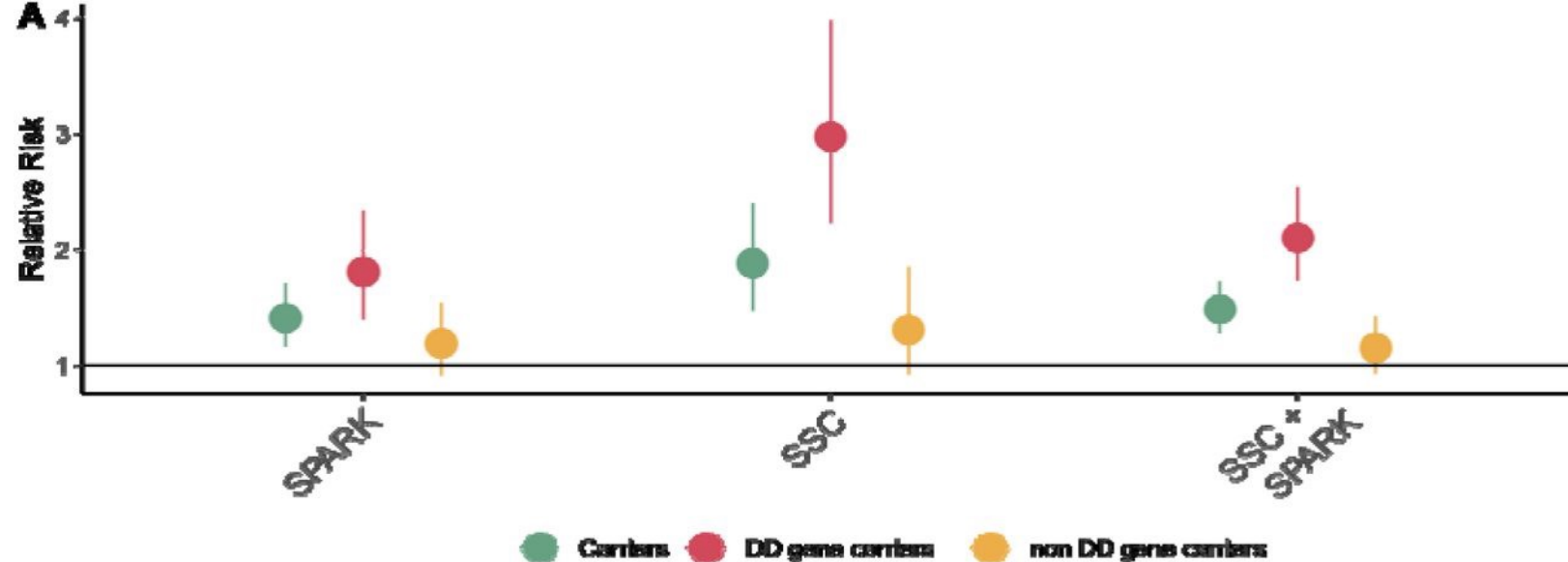
Convergence between autistic brain features and (multivariate) brain sex/gender features informs specific neurodevelopmental mechanisms

Multivariate structural brain features show lower sex-prediction accuracy in autistic females
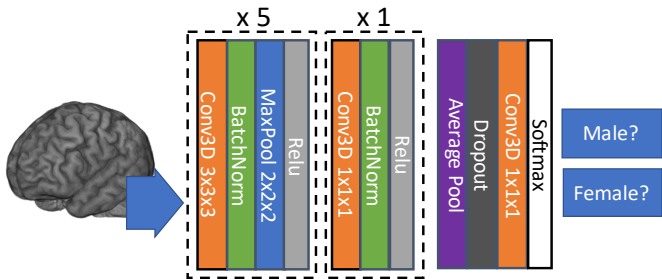
H1: In autism group, the *Simple Fully Convolutional Network* sex-prediction model is more likely to misclassify females as males, than misclassify males as females

H2: In females, the model is more likely to misclassify autistic females as males

H3: In males, the model is more likely to correctly classify autistic males to be males

Floris, Peng et al., 2022, *medRxiv*
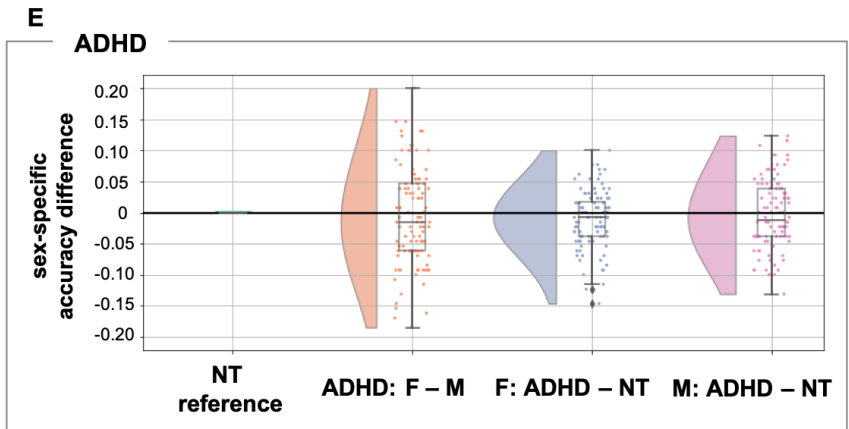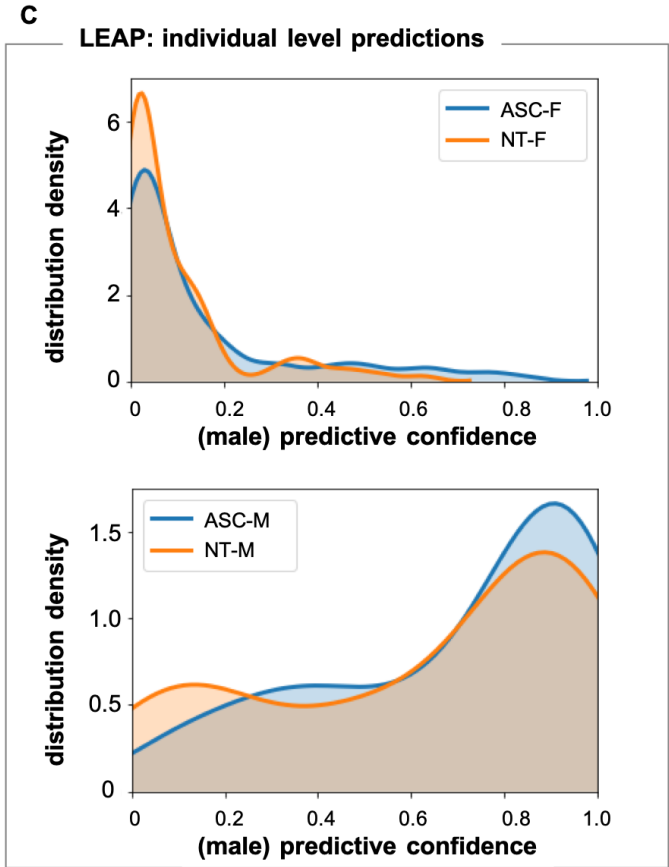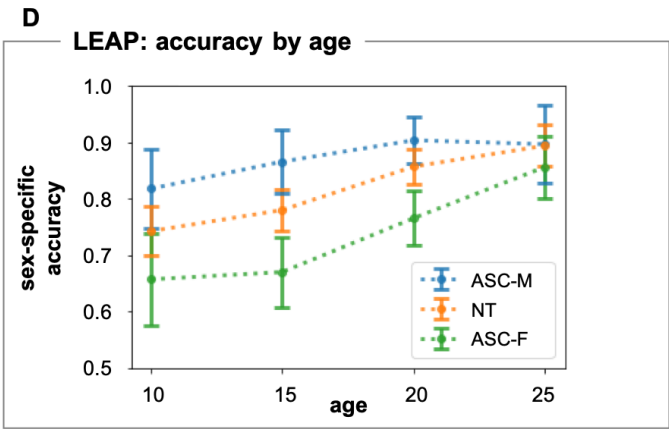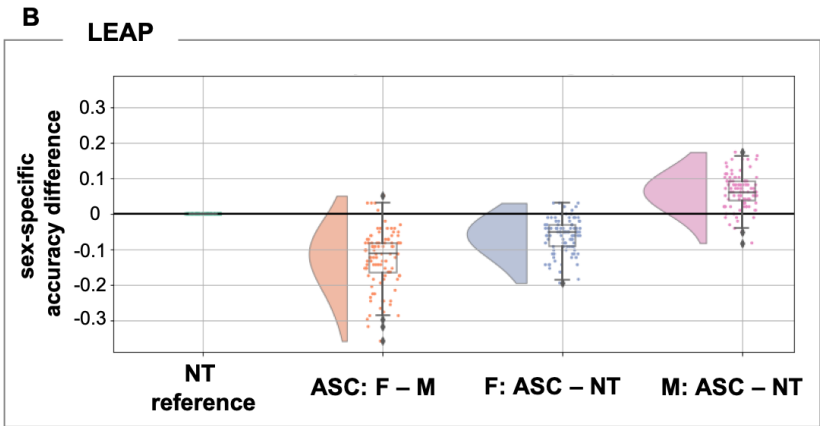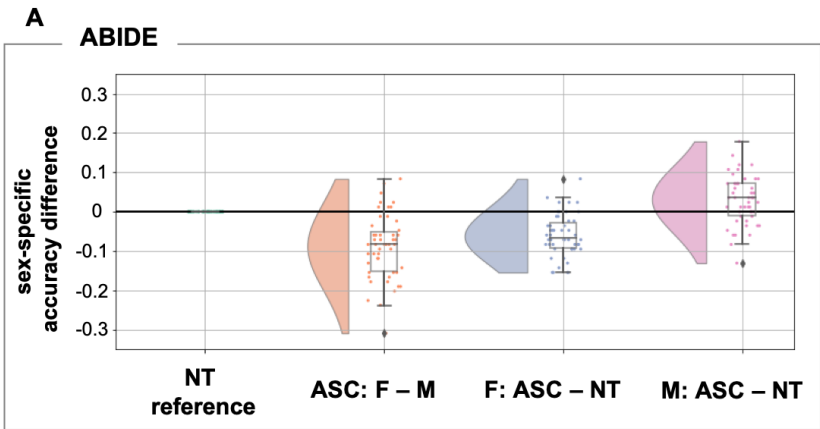
At the molecular – genetics level: what point do sex effects intersect with autism aetiology?
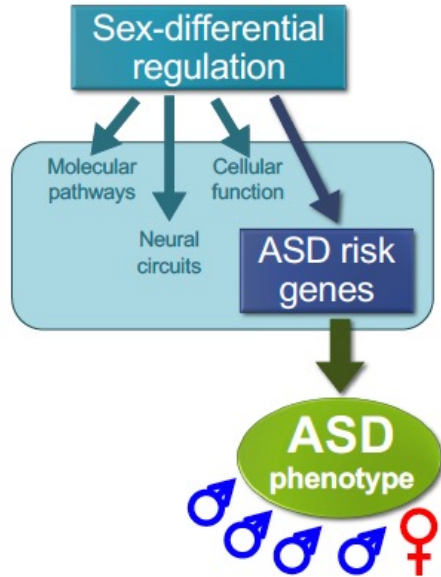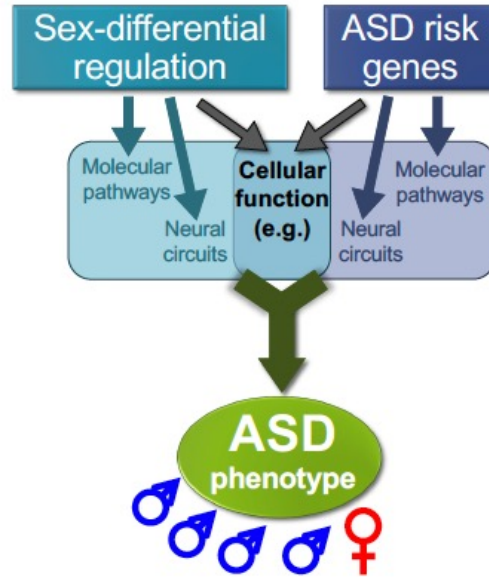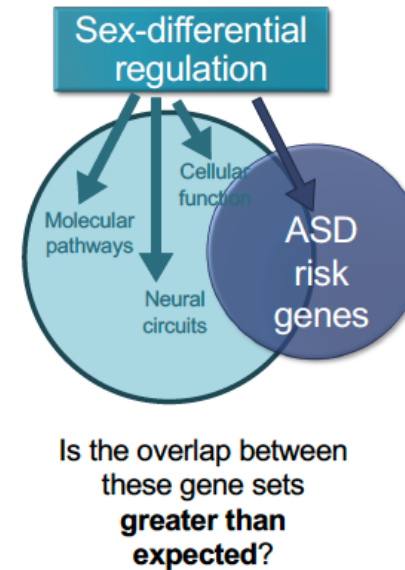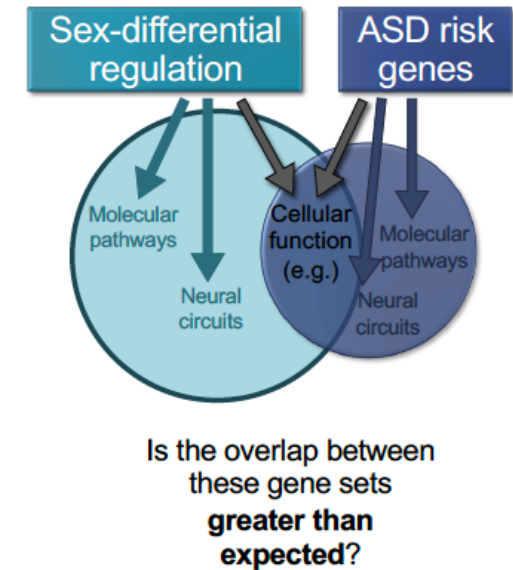
Male-biased expression genes do not overlap with autism candidate genes, but male sex-biased pathways were also implicated by the autism candidate genes (e.g., up-regulated immune/microglia genes)
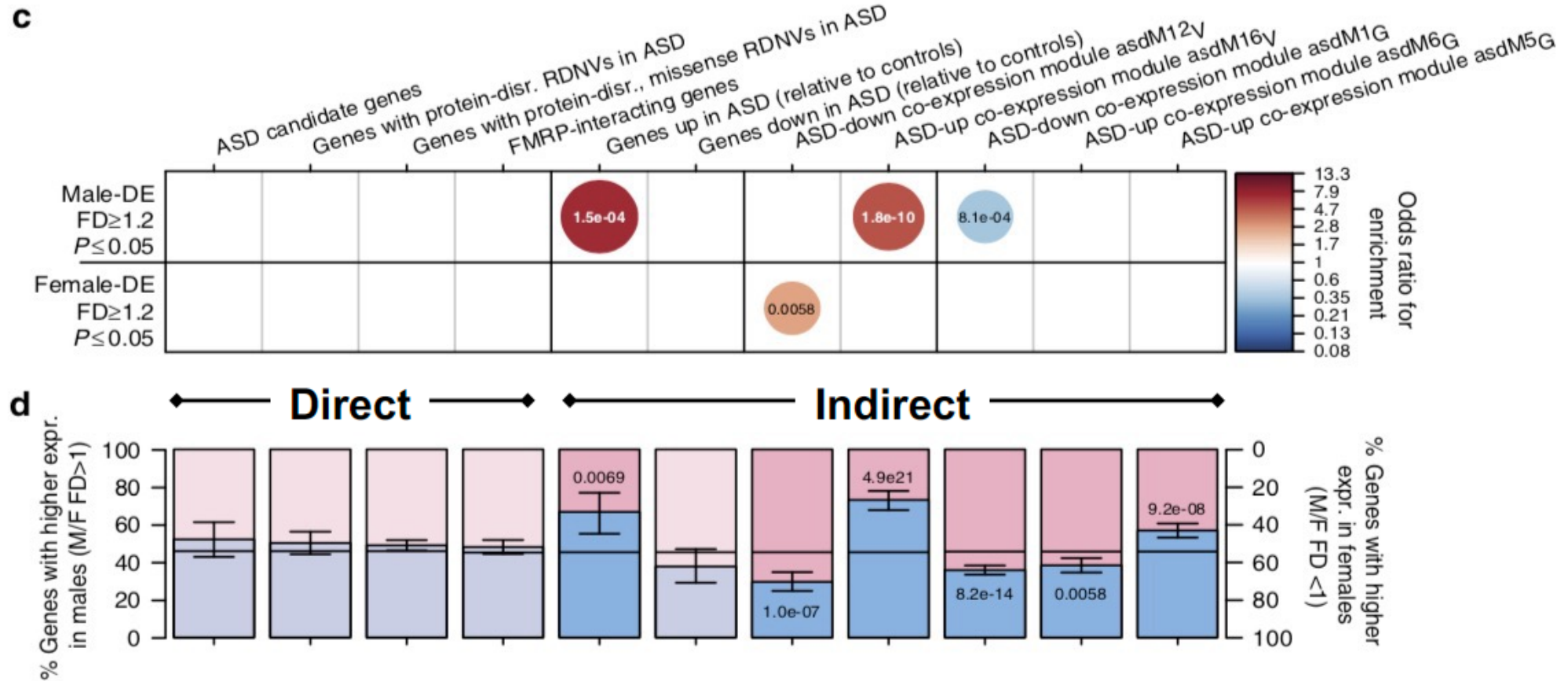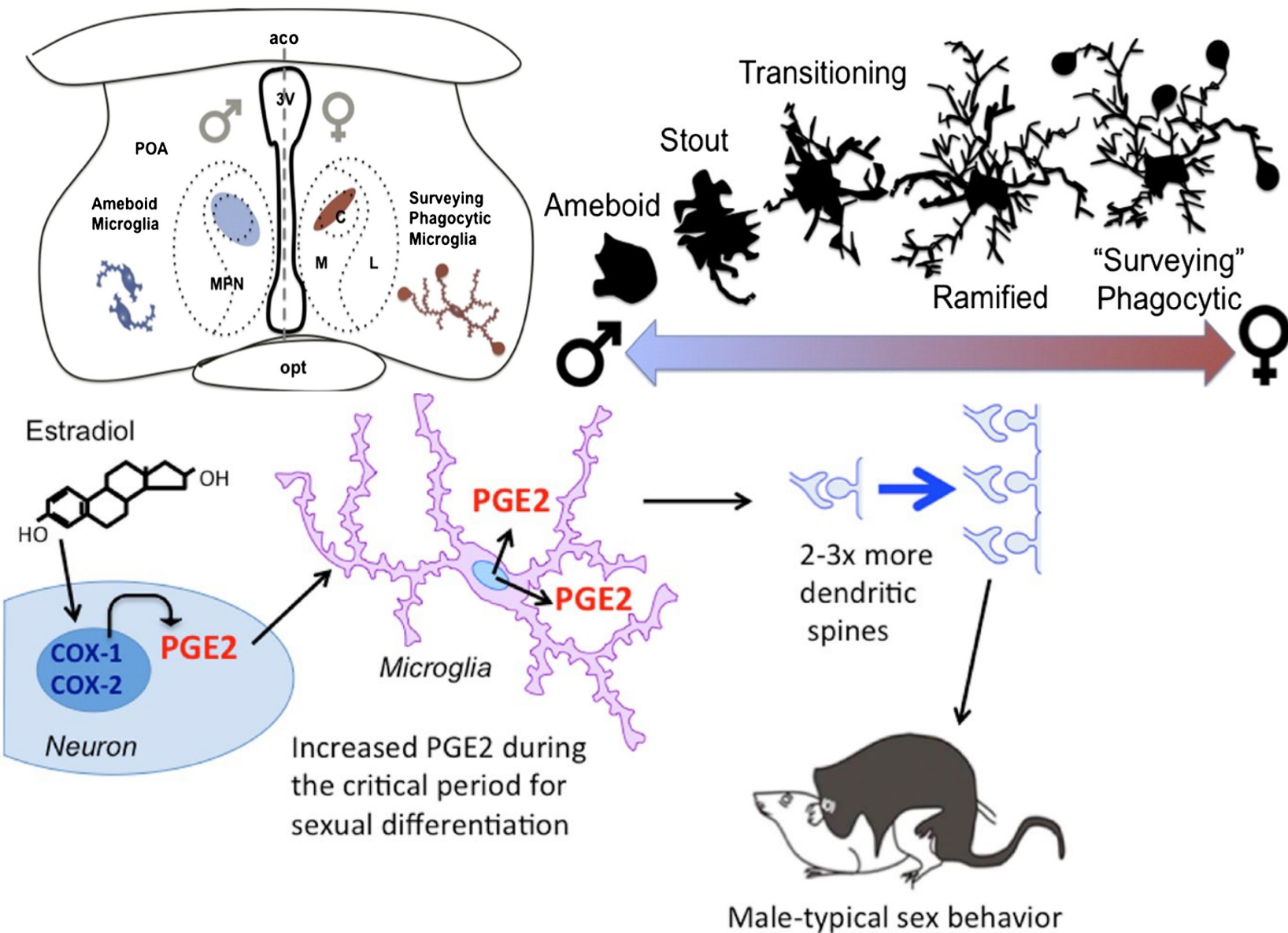
Ziats et al., 2013, *Mol Autism;* **Werling et al., 2016, *Nature Comm***
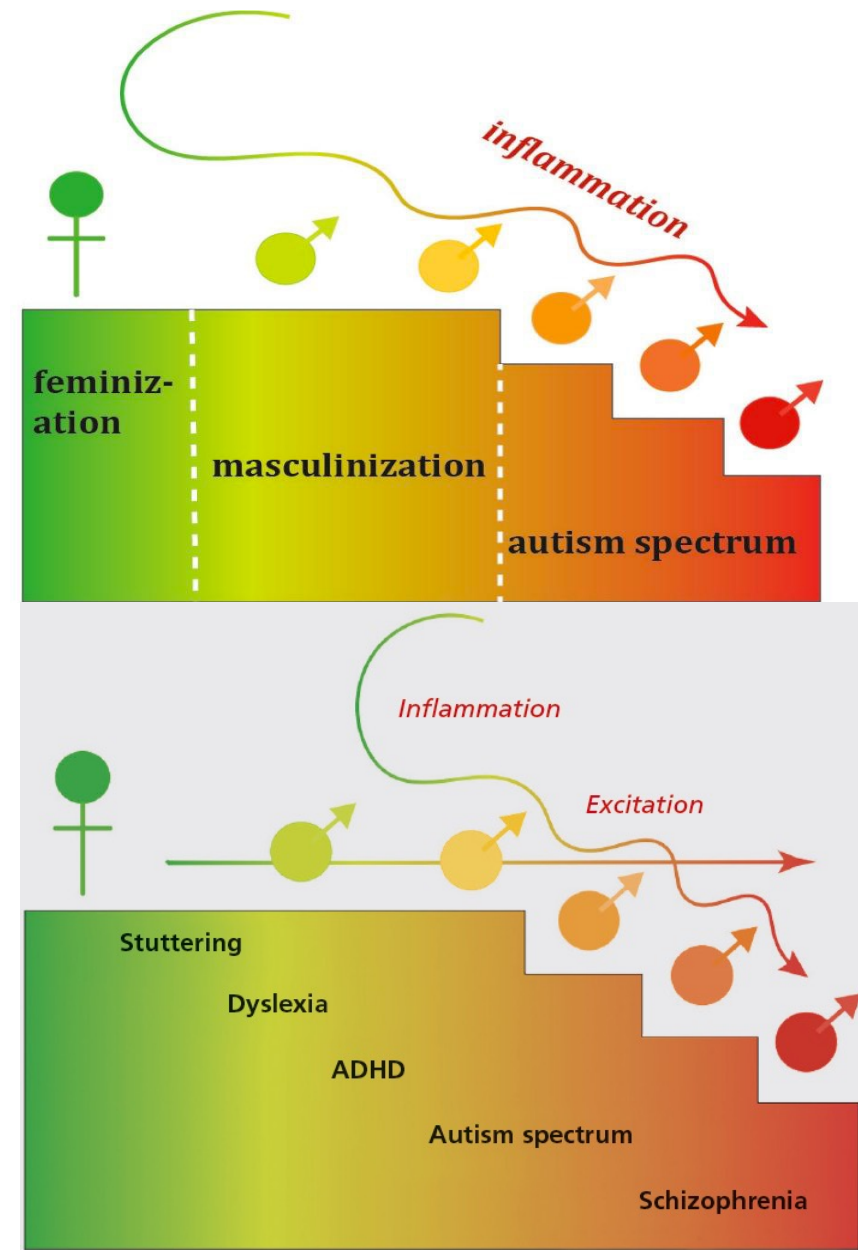
What is the nature of 'female-protection' **in the brain**?

We do not know yet. (1) Although sex- and gender-related mechanisms provide insight, we know too little about how these mechanisms influence brain development <u>before</u> the emergence of autism. (2) <u>Population-based continuum designs</u> and <u>genetics-first approaches</u> are needed.

In RATSS twin sample, for a similar increase in autistic traits, females presented with both distinct and more structural brain alterations compared to males.
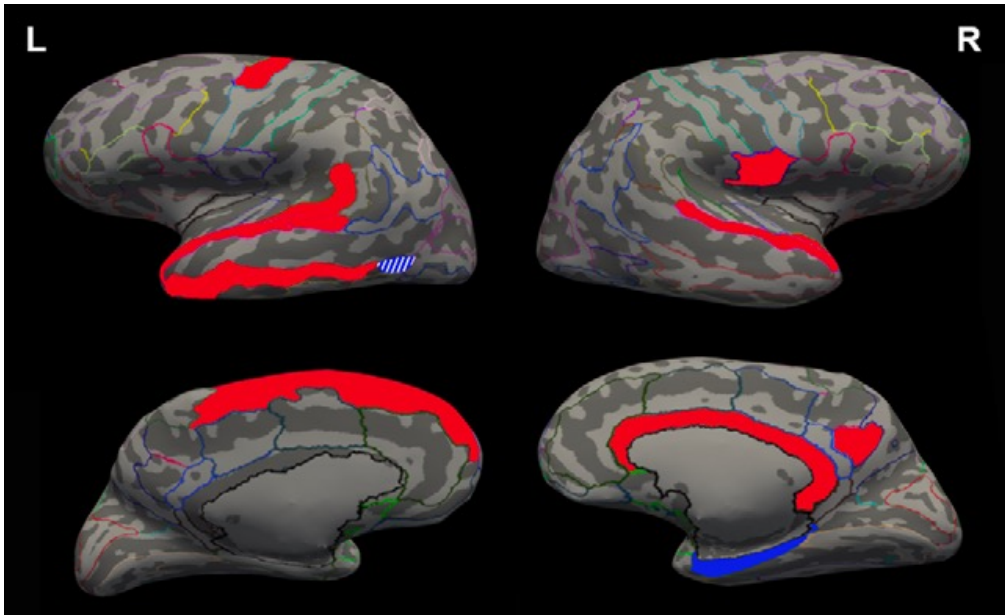
Lack of sex difference in 16p11.2 CNV gene dosage on brain volume

Cauvet et al., 2018, *Cereb Cortex*   Martin-Brevet et al., 2018, *Biol Psychiatry*
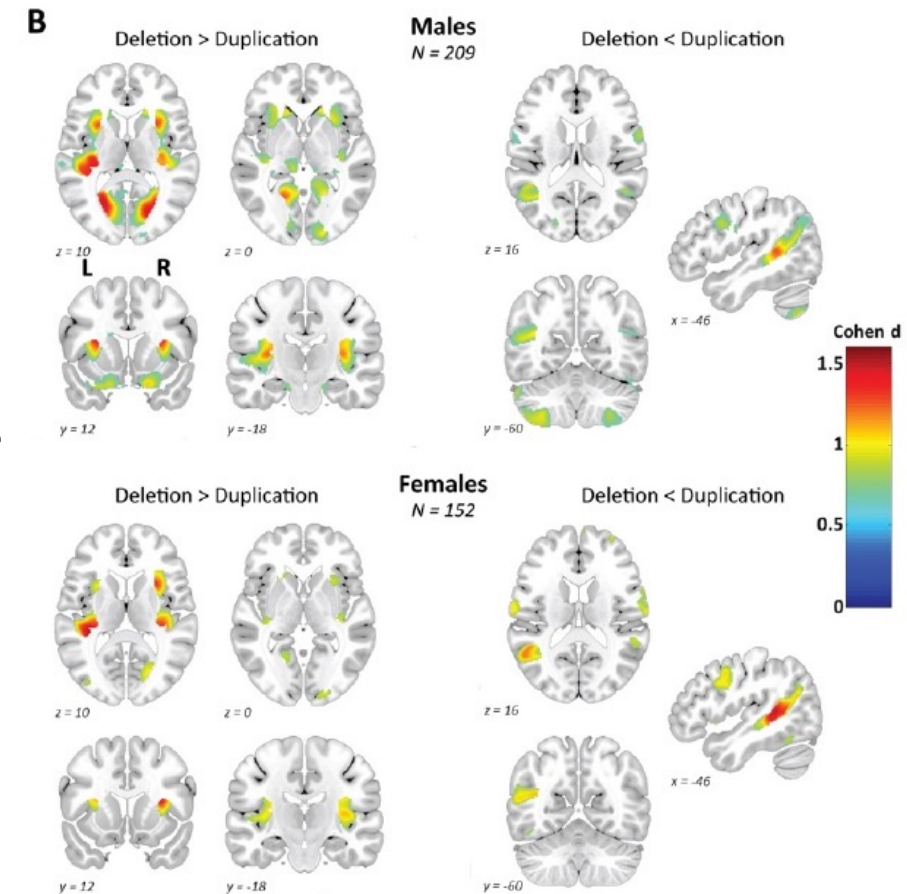
Where do we go from here?

BE SPECIFIC: SEX AND GENDER ARE MULTIDIMENSIONAL AND INTERCONNECTED
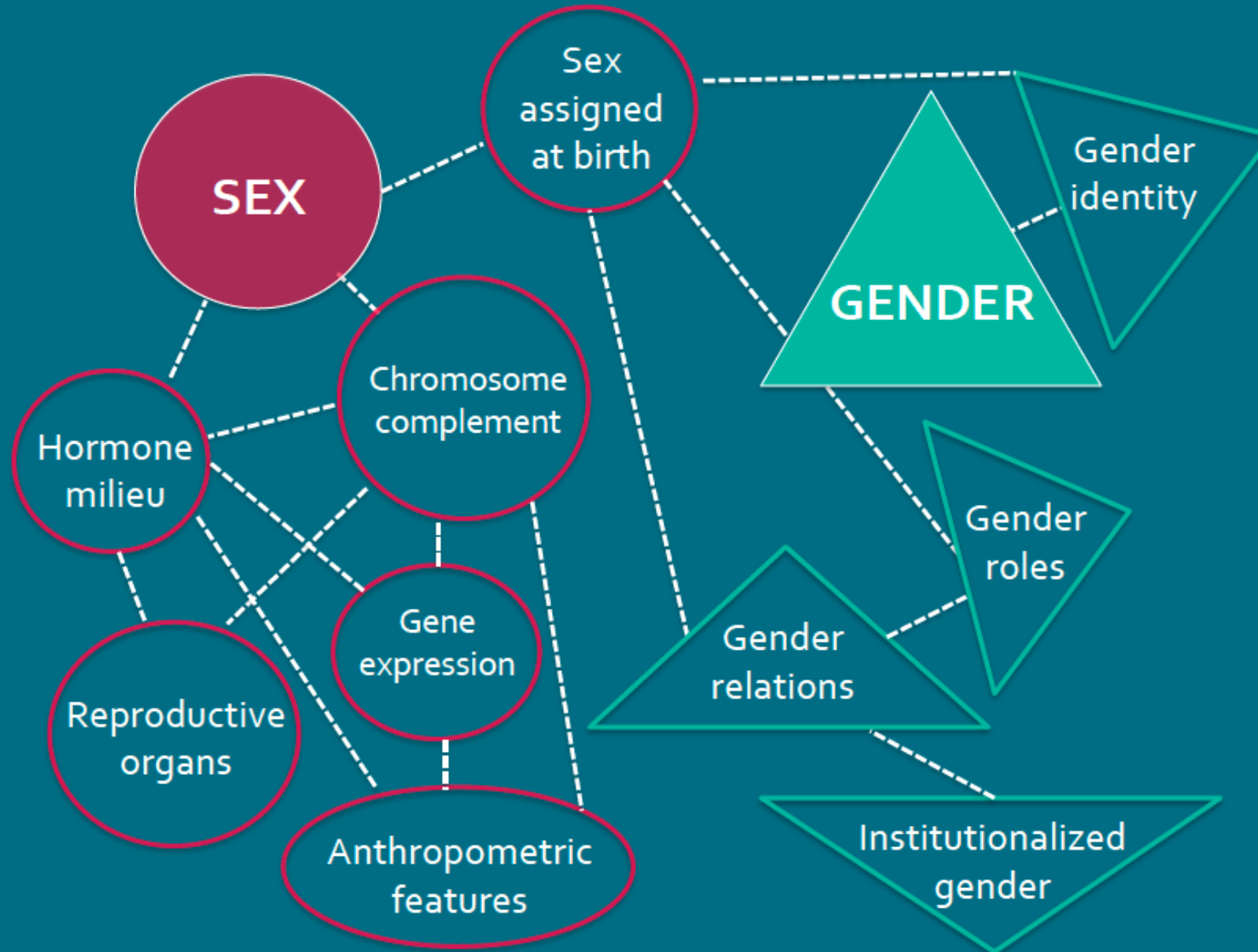
Courtesy of CIHR Institute of Gender and Health

Rethinking (& re-defining) autism; Improving recognition

~~Female autism phenotype?~~

<u>Nuanced</u> autism presentations modulated by sex- or gender-related factors

Lai, Lin, & Ameis, 2022, *Curr Opin Psychiatry*

Human beings grow and develop; Environment and contexts matter

Lai, Lombardo et al., 2017 & 2019, *Autism*
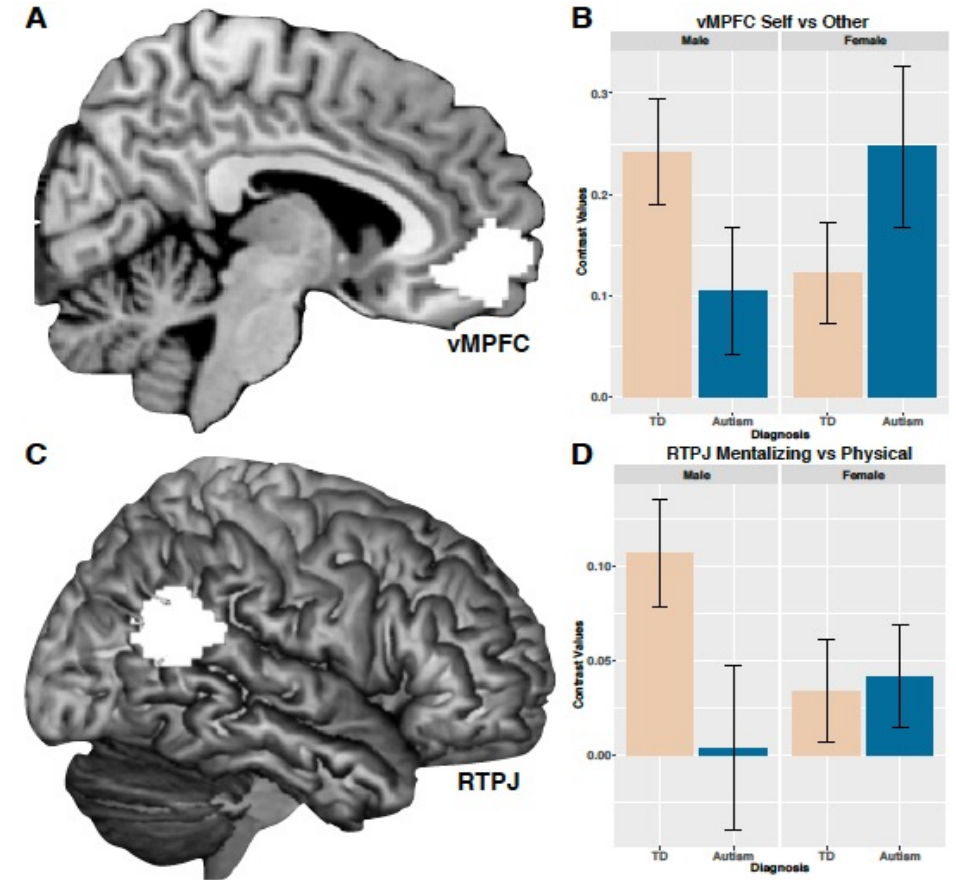
Addressing existing knowledge and practical biases; Considering intersectionality
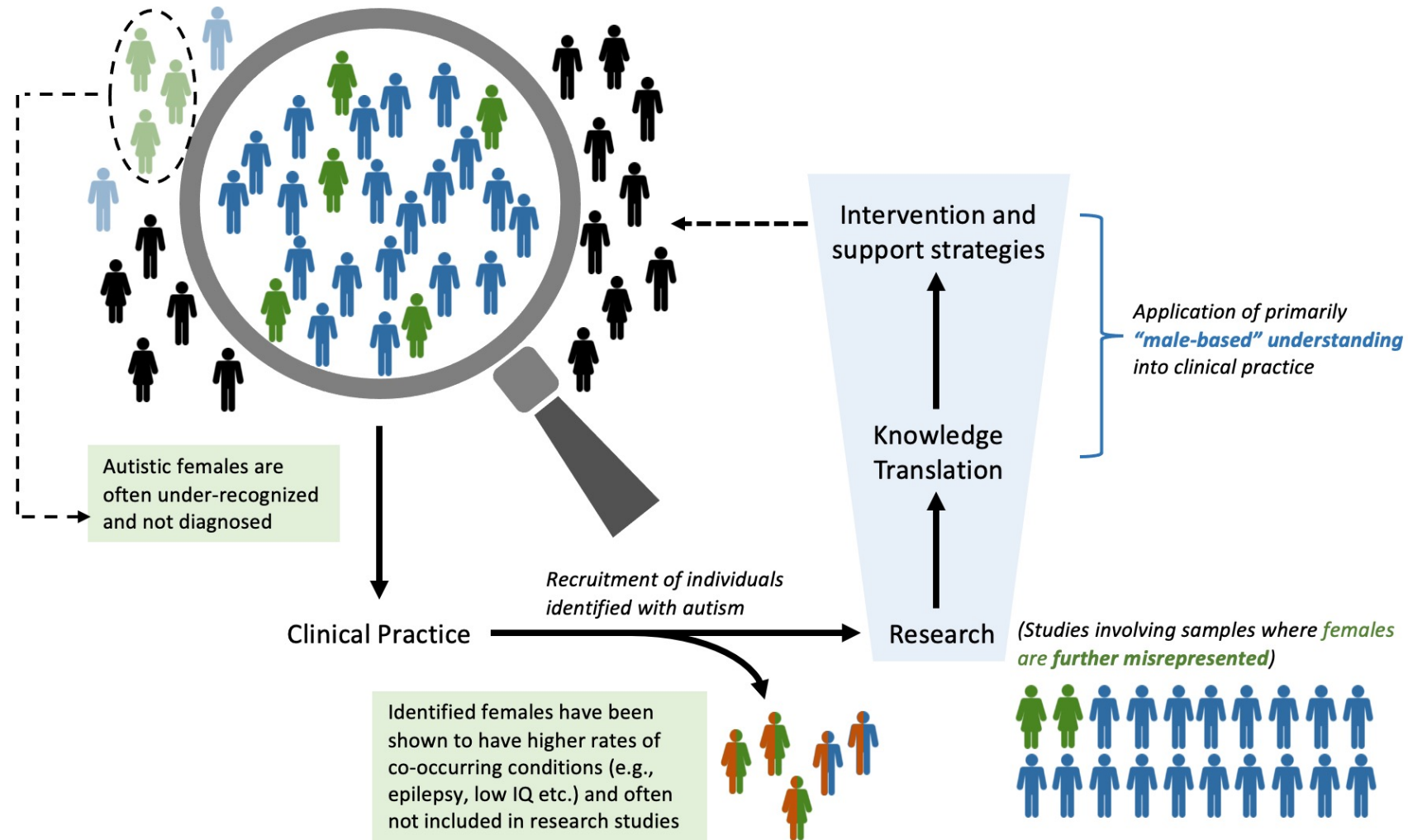
Why should we care about sex & gender in autism?

Clinical care (diagnosis, behavioural presentation, health status, supports)

Biological heterogeneity

Aetiologies

How do sex & gender modulate recognition, presentation, adaptation & developmental changes?

(How) Are the biological substrates of autism differ by sex & gender?

What underlies 'female protection'?

Are there converging mechanisms underlying sex differentiation, gender socialization, & the emergence of autism?

Sincere thanks to everyone who cares about autistic people and contributes to science 🙏