Phenotypic differences between males and females with autism spectrum disorders (ASD)

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Outline

- State of current knowledge
  - Discrepant findings
  - Methodological limitations

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(CONFUSED)

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- Moving forward
  - Donna, Kevin, and Alison

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- State of current knowledge
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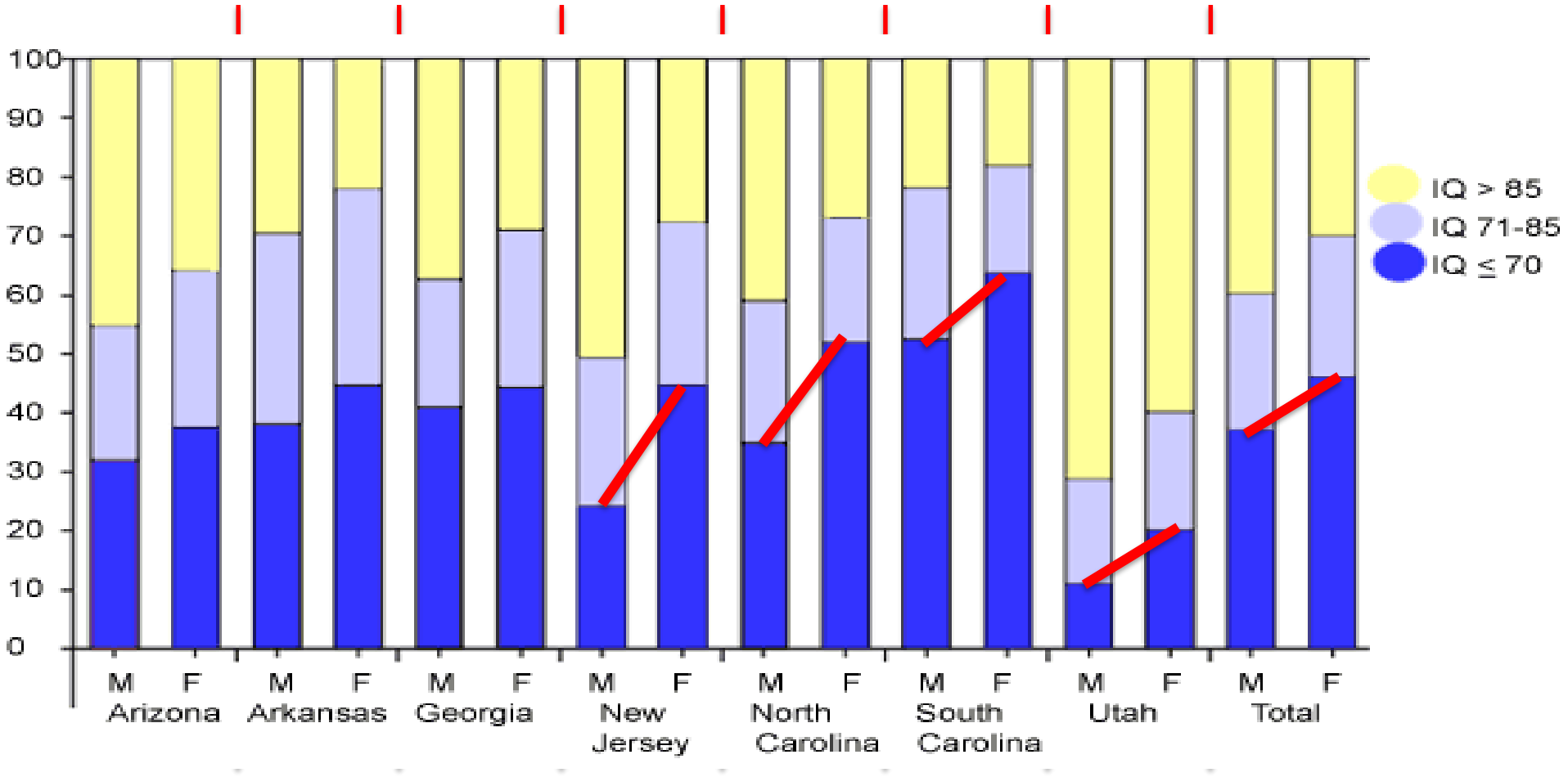
- Moving forward
  - Alison, Donna, and Kevin

(HOPEFUL FOR THE FUTURE!)

Mix of consistencies and inconsistencies

- More males with ASD than females
  - Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)
- Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end



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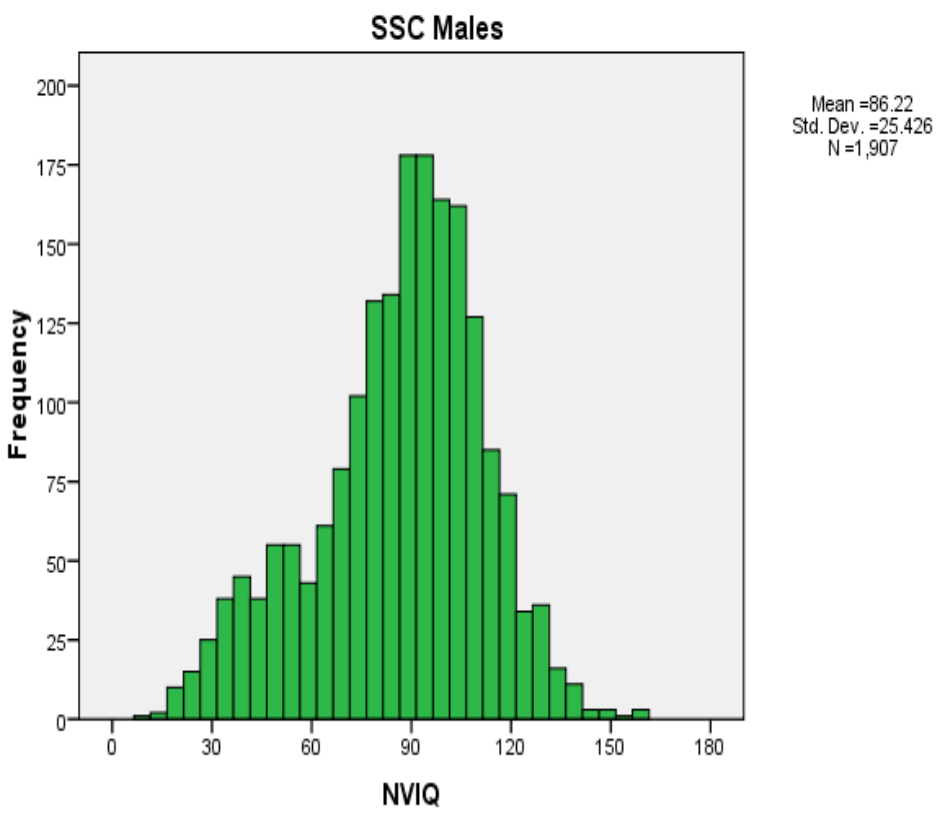
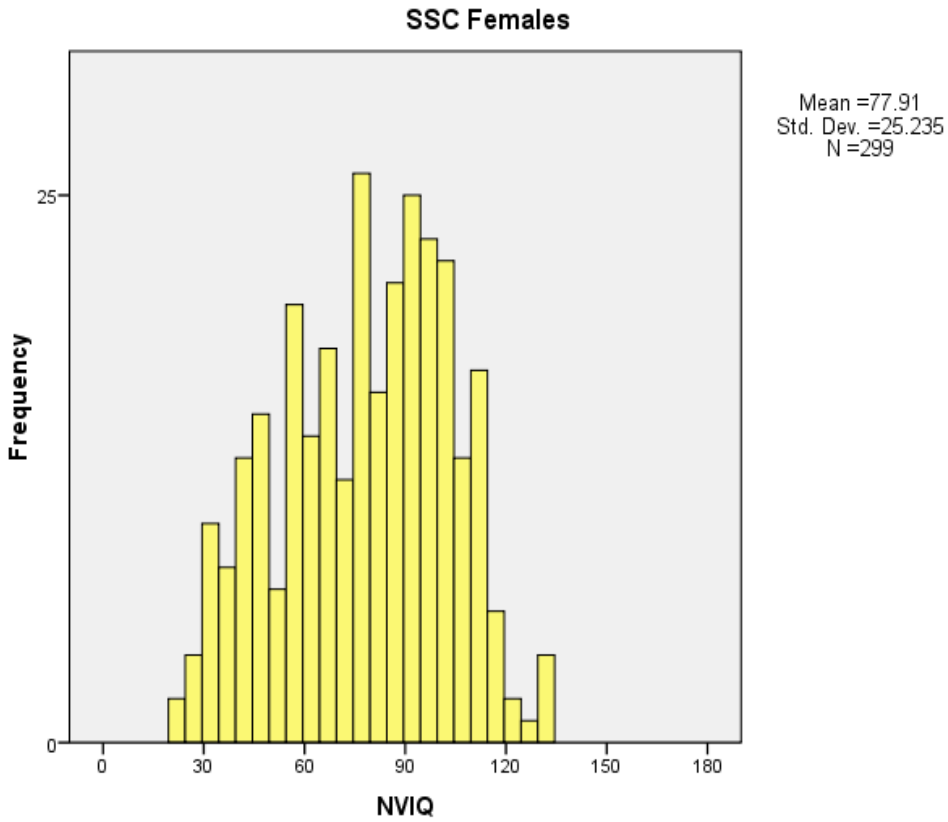
Nonverbal IQ: Simons Simplex Collection





Mix of consistencies and inconsistencies

- More males with ASD than females
  - Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)
- Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end
- Longstanding interest in examining sex differences
  - Discrepant findings related to phenotype

Social-communication

- Similar levels of ASD symptoms (Lord et al., 1982)
- Toddler/preschool boys had higher language, motor and social-competence (Carter et al., 2007)
- Preschool girls had fewer social-communication impairments (Zwaigenbaum et al., 2012)
- Adult females had fewer social-communication difficulties (Lai et al., 2011)
- Girls had fewer teacher-reported behavior problems (Mandy et al., 2012)

Restricted and repetitive behaviors

- Females exhibited lower repetitive behavior scores (e.g., Hartley et al., 2009; Mandy et al., 2011; Frazier et al., 2014)
  - Seen across multiple measures (3Di, ADI-R, RBS-R, ADOS)
- No sex differences in community-based sample of 288 toddlers with ASD (54 girls) (Reinhardt et al, 2014)

Questions persist

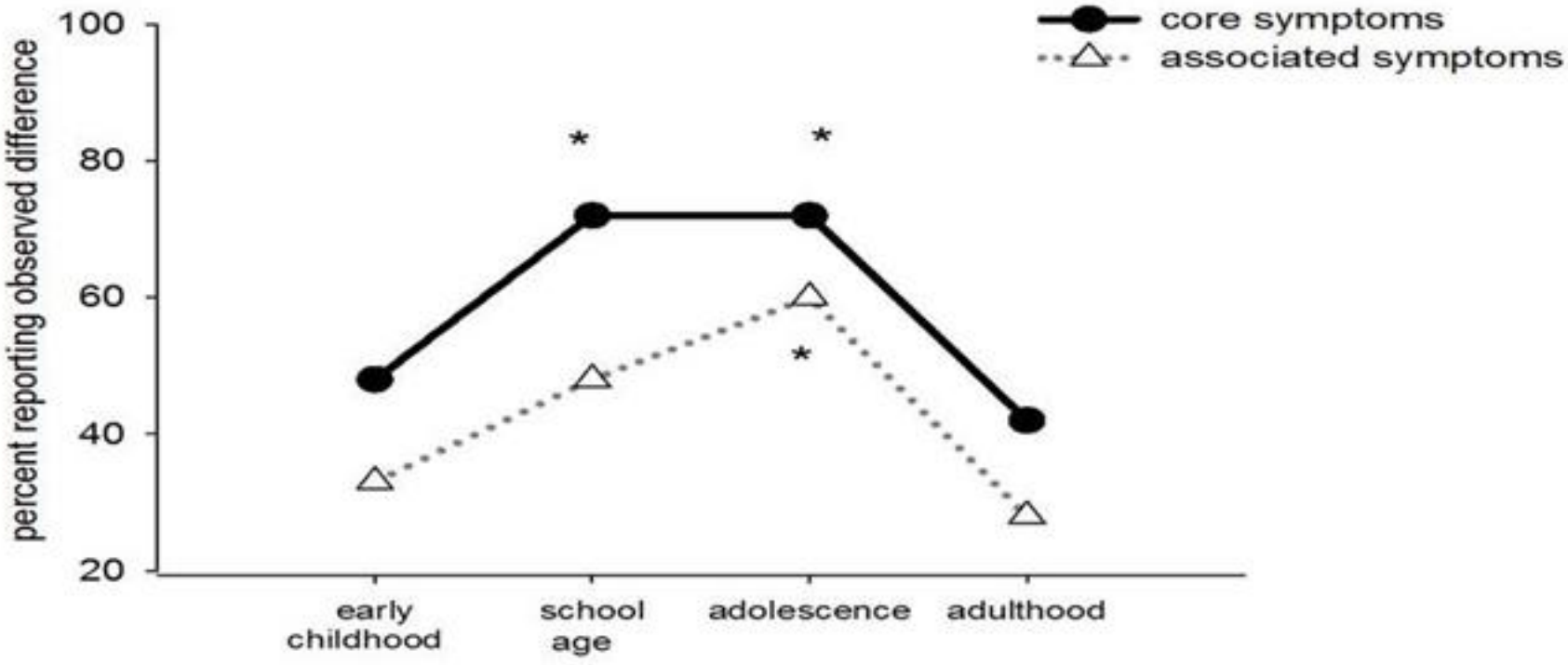
- Clinicians and researchers continue to wonder (and worry) about sex differences in behavioral manifestations of ASD

Clinician perceptions

Gender	Female: 86% (n=91)	Male: 14% (n=15)		
Involvement in dx	57% make dx (n=58)	31% perform assessments (n=32)	12% participate in evaluation (n=12)	
Years experience	58% have 10+ years (n=56)	26% have spent 6-9 years (n=25)	13% have 1-5 years experience (n=12)	3 % have less than one year (n=3)
Primary age range seen	7% see mostly adults (n=7)	9% see primarily adolescents (n=8)	37% work with school age children (n=35)	47% see children 5 years old or younger (n=44)
Number seen per month	Mean = 15.8 people, median = 8			
Number of females seen per month	Mean = 3.4 females, median =2			

Jamison, Huerta, Bishop, & Halladay (under review).

Observed differences in core and associated symptoms



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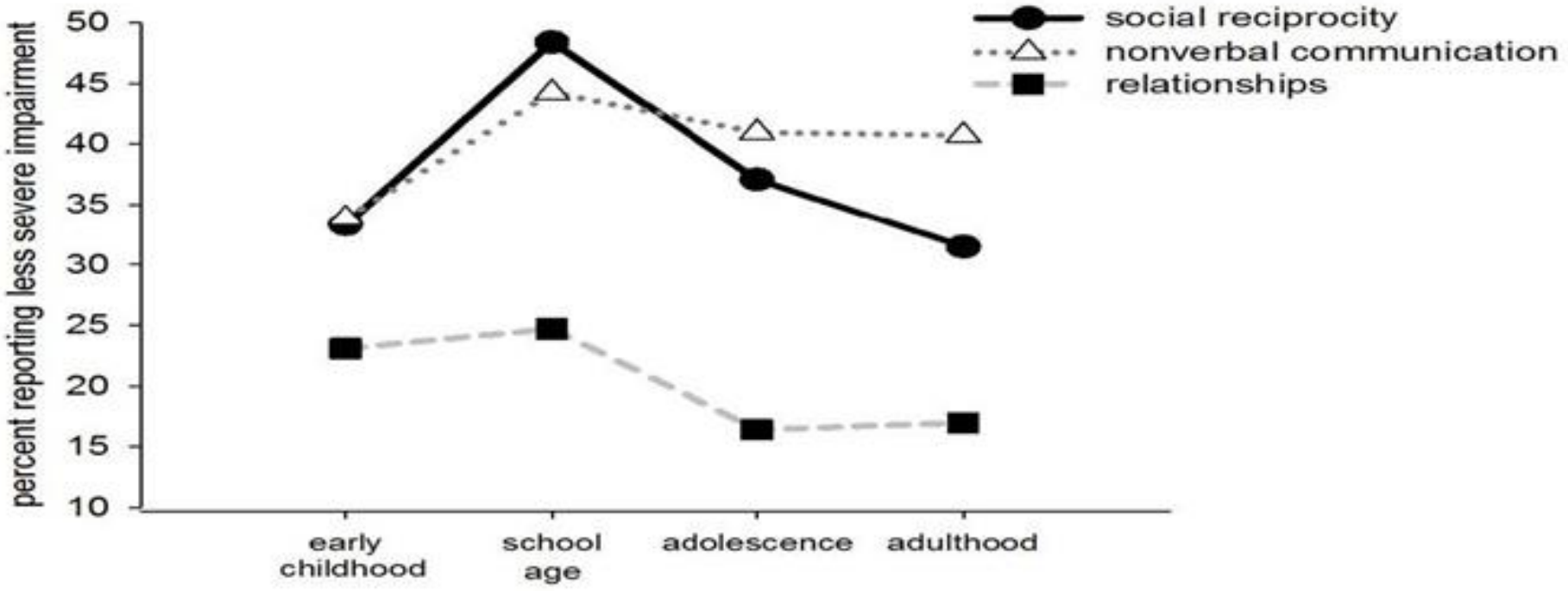
Observed differences in social-communication



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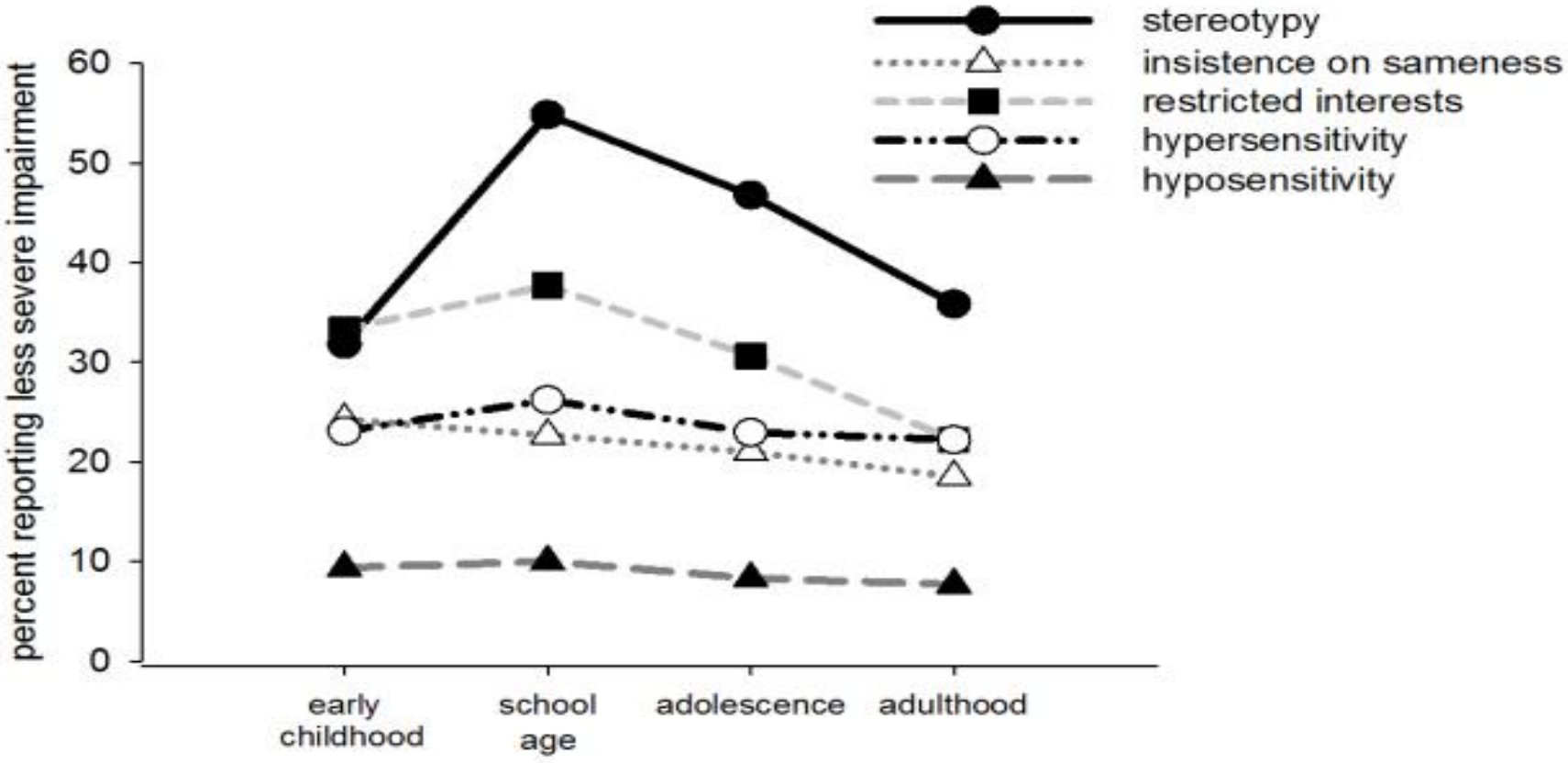
Observed differences in RRBs



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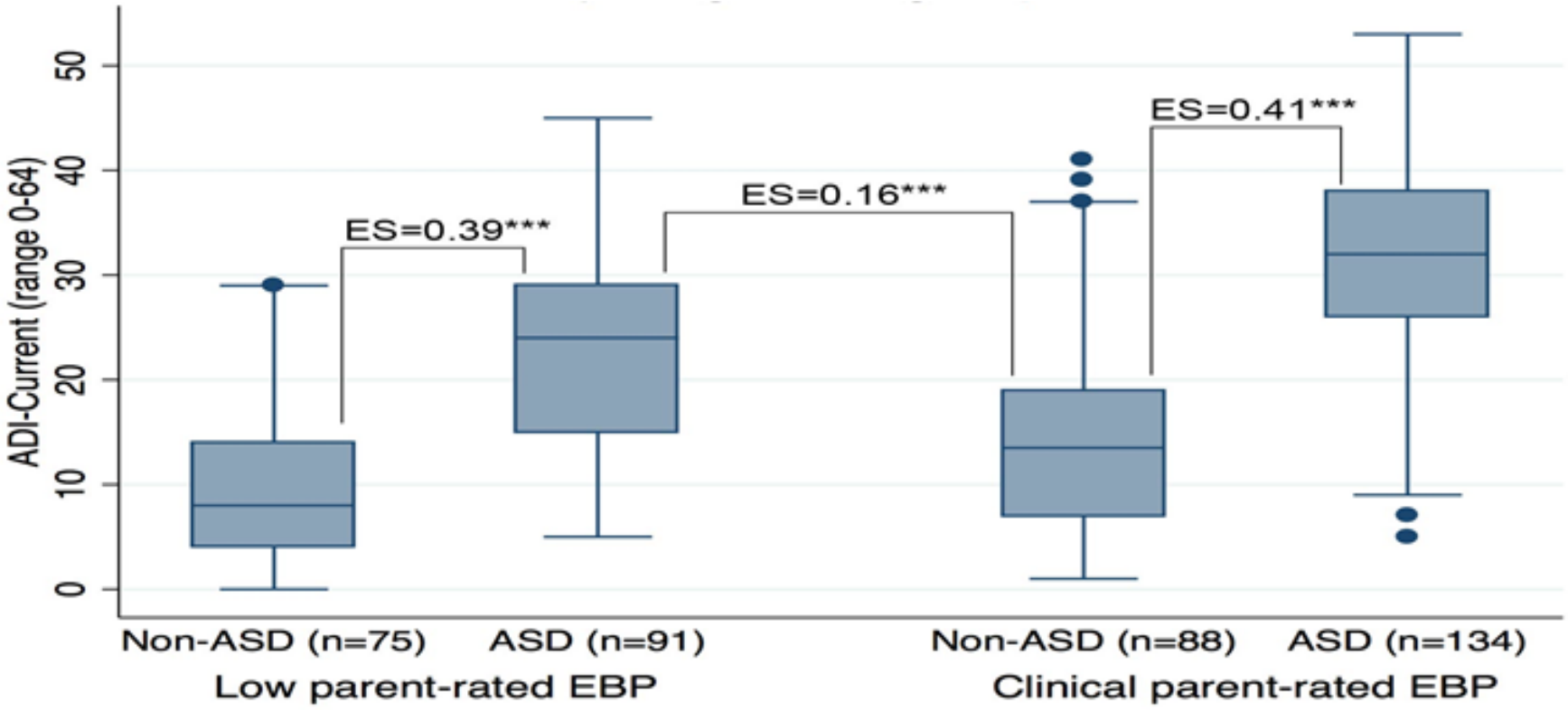
Clinical observations vs. empirical data

- Why the mismatch?
  - Measurement issues
  - Sampling issues
  - Methodological issues

Measurement issues

- Existing measures may lack sensitivity for detecting some females with ASD
  - Diagnostic constructs (which in turn are reflected on measures) could be sex-biased
- Scores on ASD measures are affected by individual factors like IQ and emotional/behavioral problems (EBP)

ADI-R scores by diagnostic group and level of EBP



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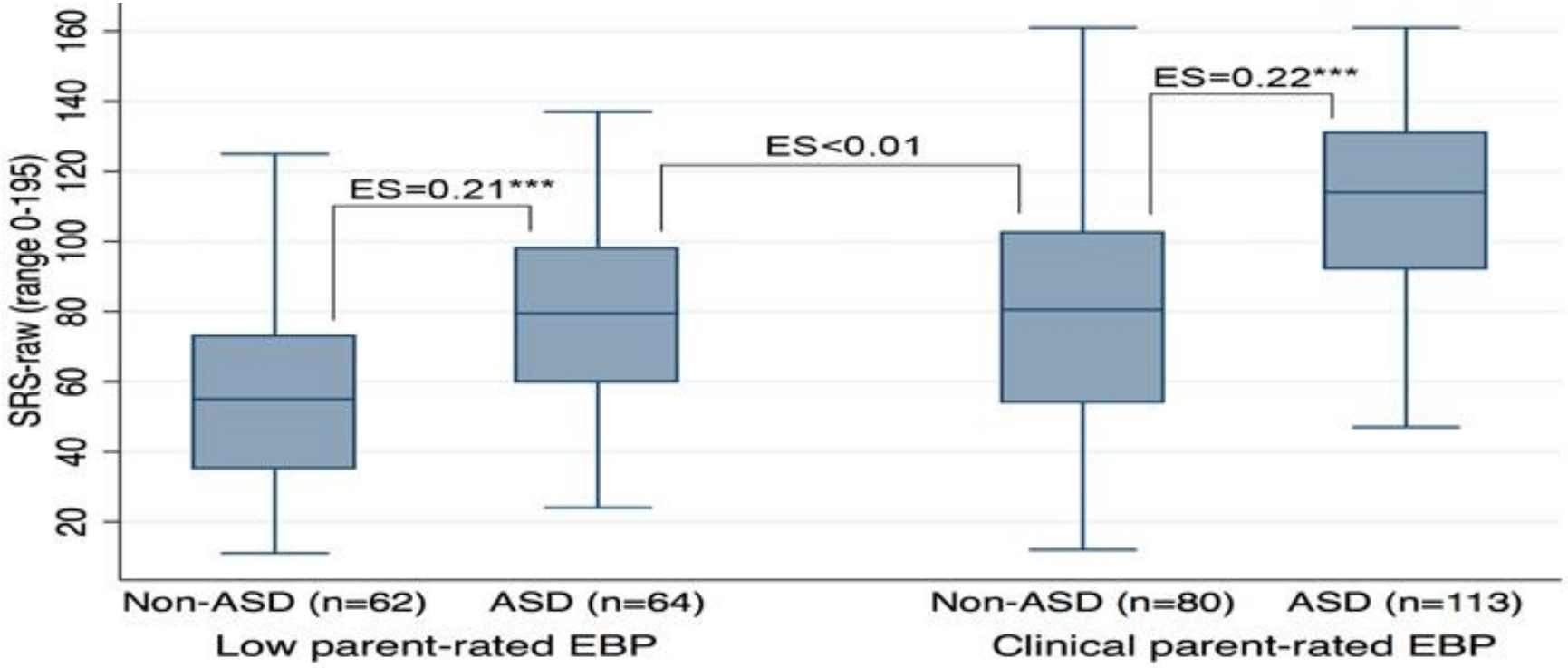
SRS scores by diagnostic group and level of EBP



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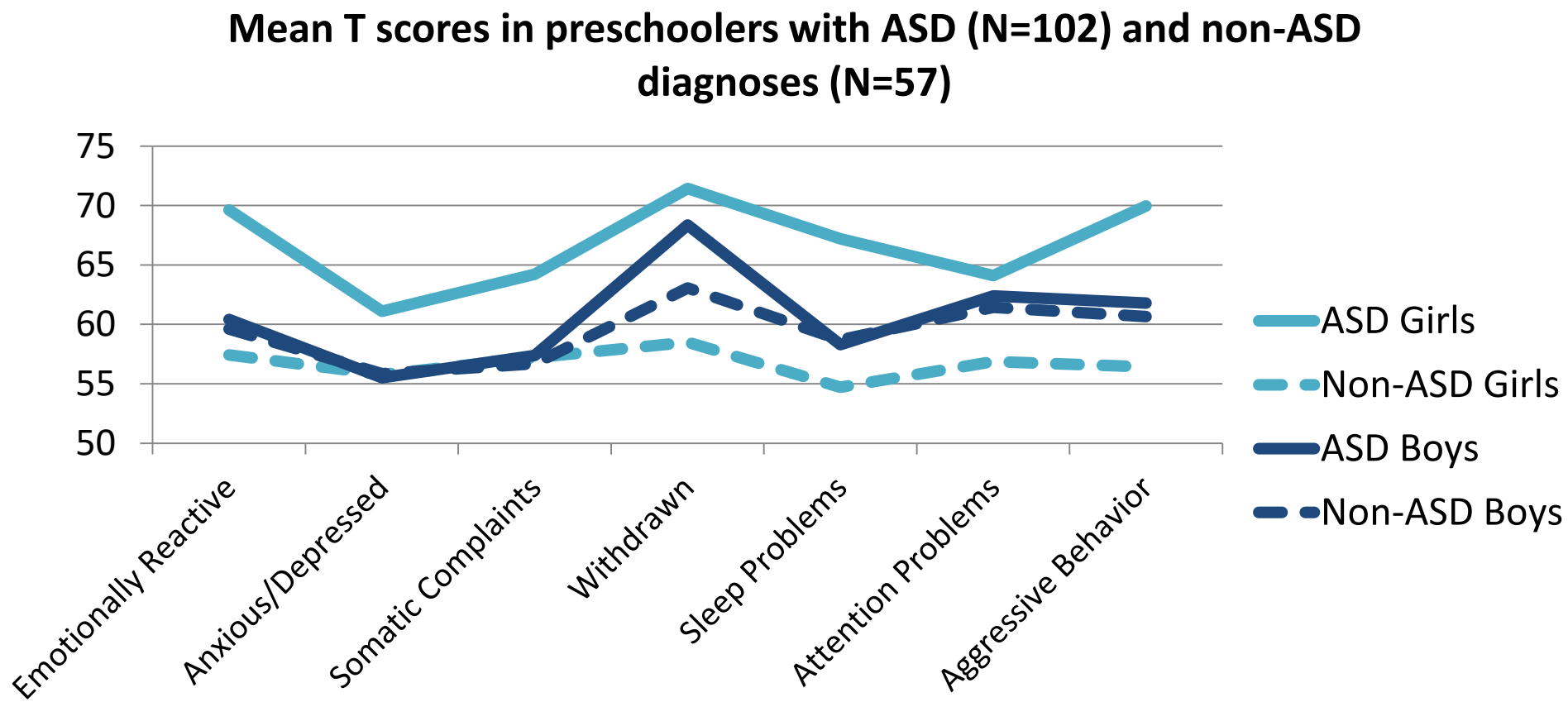
Sampling Issues

- Measurement issues can affect ascertainment
  - Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)

Referral bias



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Sampling Issues

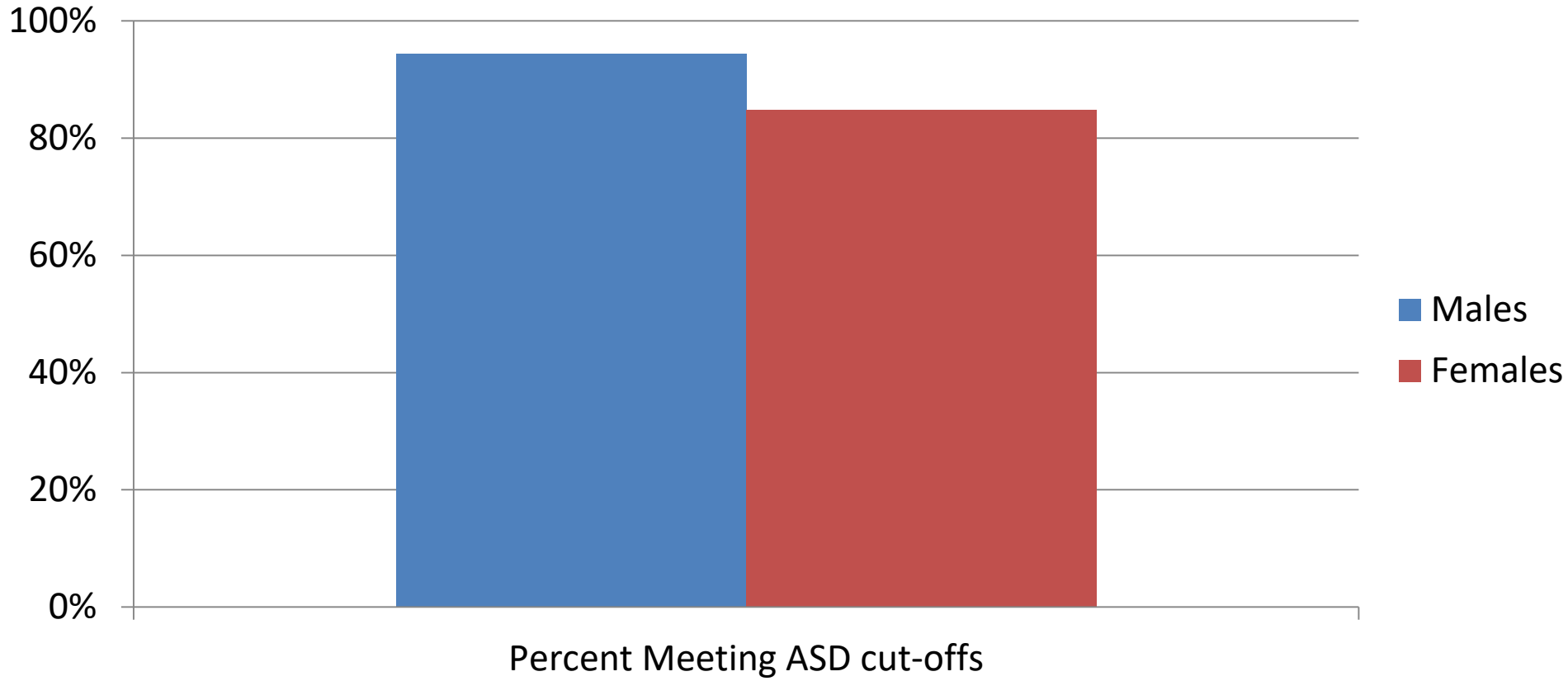
- Measurement issues can affect ascertainment
  - Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)
- Small clinical samples
  - Ns for females are particularly small
  - May not be powered to properly account for other important individual differences

School-aged/adolescent; verbally fluent

	Male	Female
Number of Participants	396	85
Age in years, *M (SD)*	8.9 (2.9)	8.7 (2.8)
VIQ, *M (SD)*	99.6 (18.9)	104.6 (16.7)
NVIQ, *M (SD)*	104.7 (15.5)	104.3 (14.8)

Bishop, Sweeney, Huerta, Havdahl, & Lord (unpublished).

ADOS-2 Module 3 ASD classification



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Calibrated severity scores (CSS)

- Controlling for VIQ and age, sex significantly predicted:
  - Overall CSS (*B*= -.57, CI 95% -1.08 to -0.06, *p*= .03)
  - RRB Domain Calibrated Scores (*B*= -.89, CI 95% -1.4 to -.34, *p*= .002)

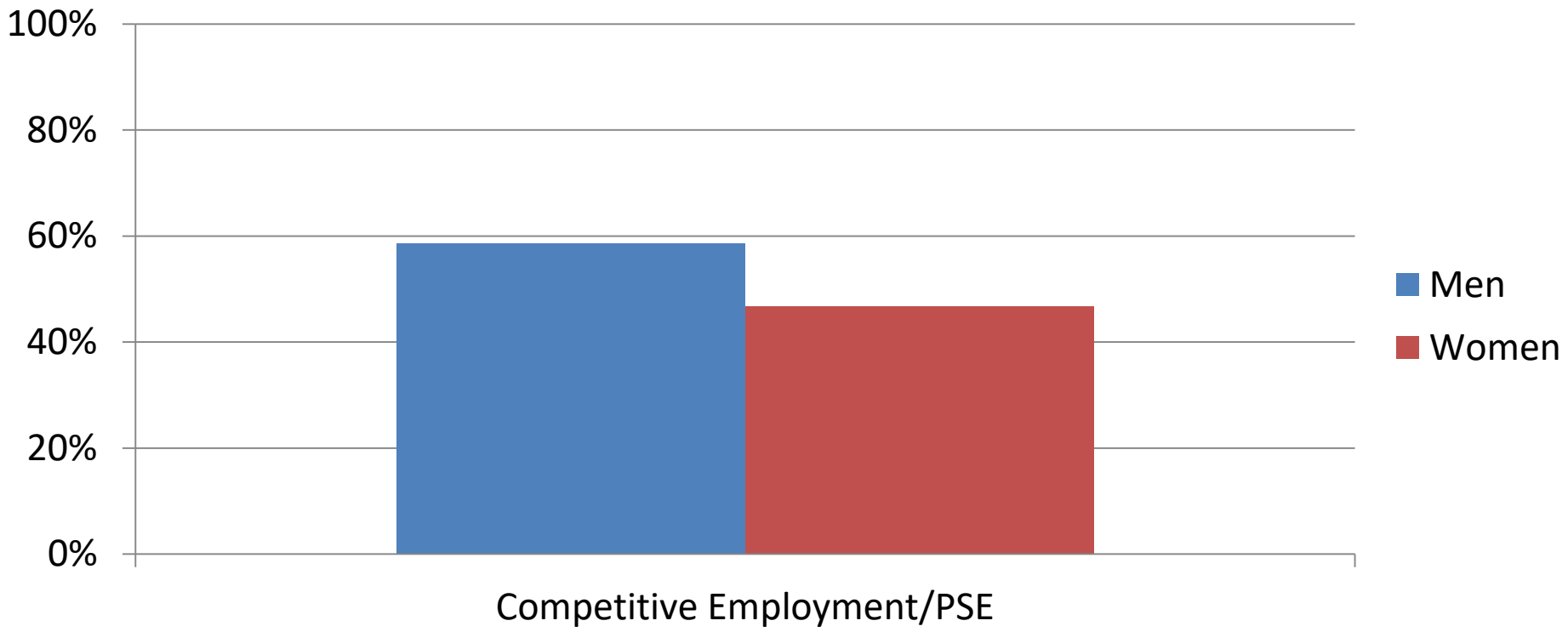
- In this sample, even females with lower scores (including those who scored below instrument cut-offs) still received best-estimate clinical diagnoses of ASD

Bishop, Sweeney, Huerta, Havdahl, & Lord (unpublished).

Methodological issues

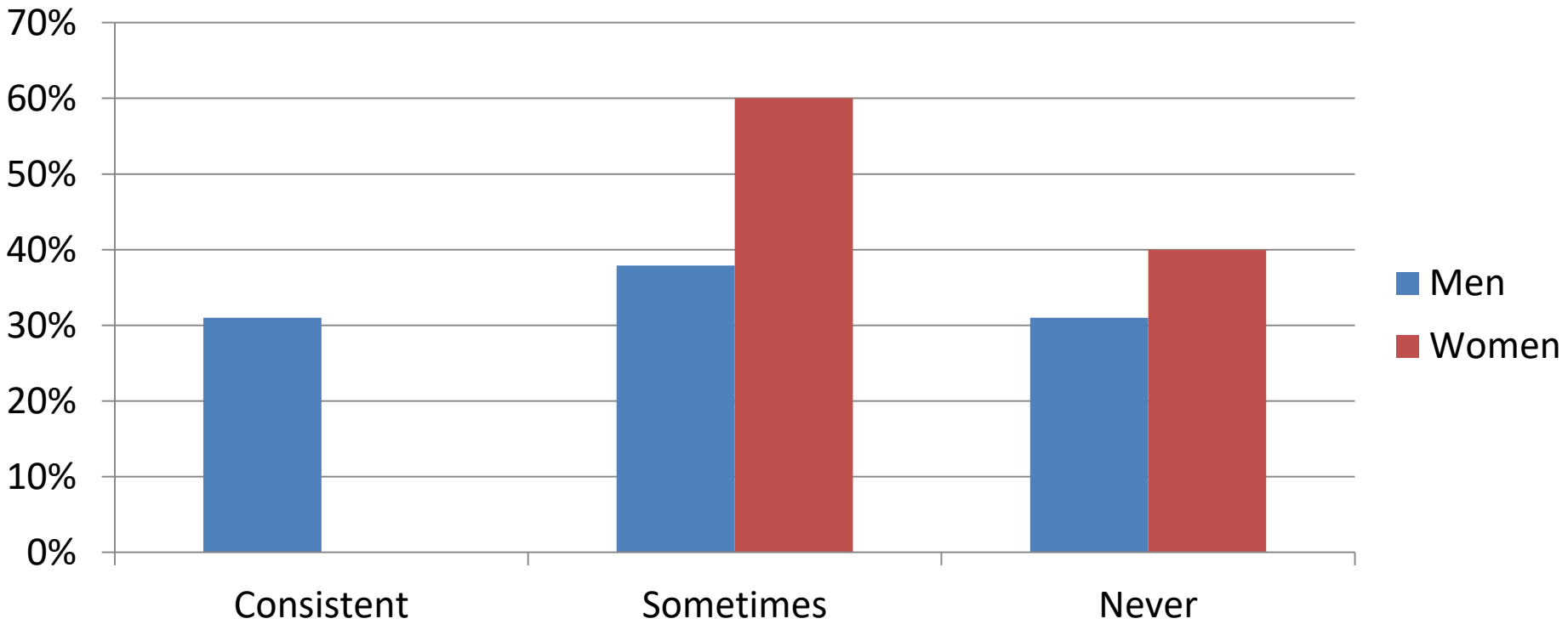
- Detecting meaningful differences relies on identification of appropriate comparison groups
  - Who is a *relevant* control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)
- Clear need for longitudinal data

Employment/PSE at the First Time Point after High School Exit



Taylor, J. L., Henninger, N. A., & Mailick, M. R. (2015). Longitudinal patterns of employment and postsecondary education for adults with autism and average-range IQ. *Autism, 19*(7), 785-793. doi:10.1177/1362361315585643

Patterns of Employment/PSE over Time



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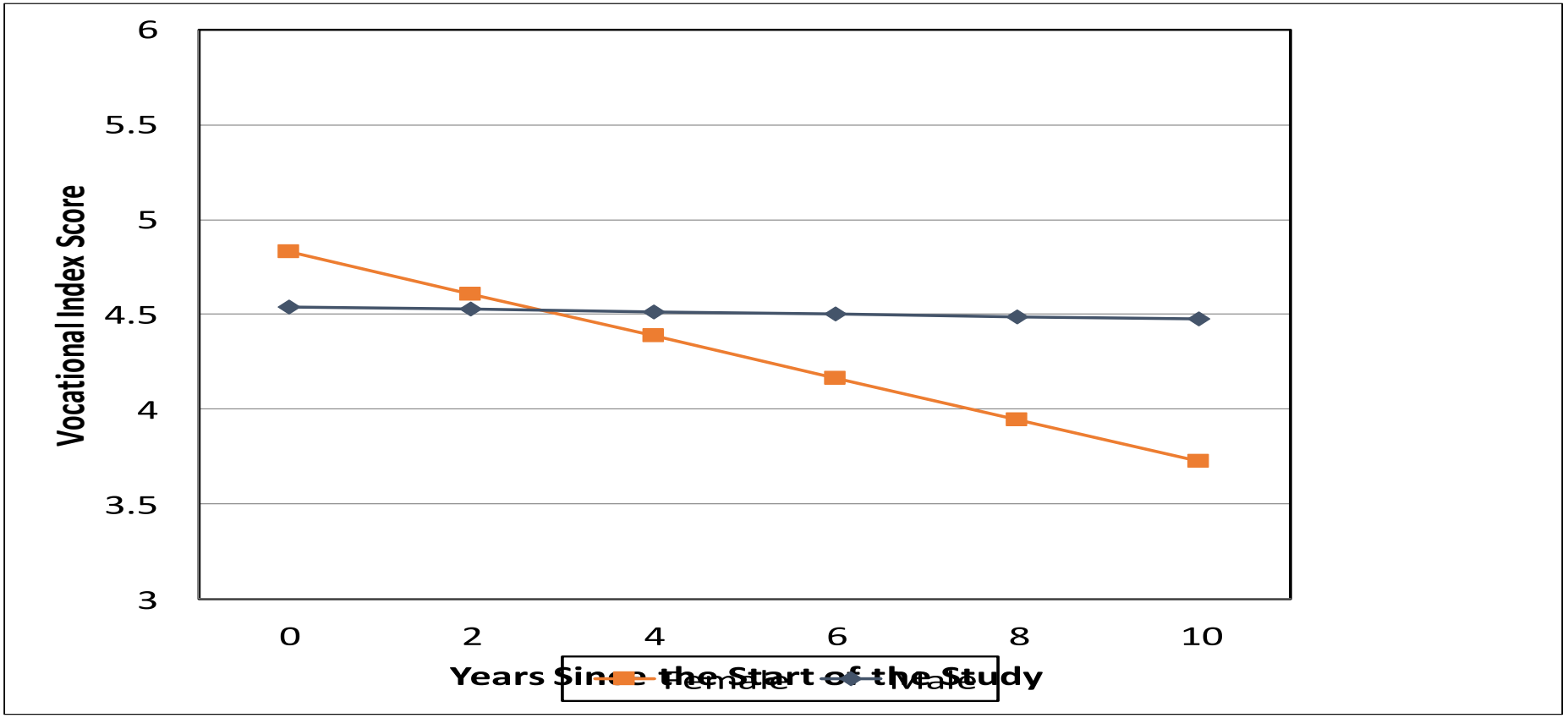
Men vs. women with ID



Taylor, J. L., & Mailick, M. R. (2014). A longitudinal examination of 10-year change in vocational and educational activities for adults with autism spectrum disorders. *Developmental Psychology, 50*(3), 699-708. doi:10.1037/a0034297

Methodological issues

- Detecting meaningful differences relies on identification of appropriate comparison groups
  - Who is a *relevant* control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)
- Clear need for longitudinal data
- Need to move existing behavioral measures
- Incorporate different measurement strategies

Conclusions

- There do appear to be at least subtle sex differences in phenotype within certain groups
  - Ascertainment and measurement issues present major challenges
- Sex is **one** stratification variable worth considering, but it needs to be considered in the context of other behavioral and biological variables that we know are important

Thank you

- **UMACC/CADB families, clinicians and researchers**
- Alycia Halladay
- Alexandra Havdahl
- Marisela Huerta
- Rene Jamison
- Catherine Lord
- Shanping Qiu
- Michael Sweeney
- Julie Taylor

EXTRA SLIDES

Direction of Clinician Responses: Early Childhoo

Criteria / Severity	Less Severe (M<F)	Similar (M=F)	More Severe (F>M)
Social reciprocity	33% (n=22)	62% (n=41)	5% (n=3)
Nonverbal behaviors	33% (n=22)	60% (n=39)	6% (n=4)
Developing, maintaining relationships	23% (n=15)	71% (n=46)	6% (n=4)
Stereotyped/Repetitive Behaviors	32% (n=21)	65% (n=43)	3% (n=2)
Insistence on Sameness	24% (n=16)	71% (n=47)	5% (n=3)
Restricted/Fixated Interests	33% (n=22)	65% (n=43)	2% (n=1)
Hyperreactivity to sensory	9% (n=6)	86% (n=55)	5% (n=3)
Hyporeactivity to sensory	17% (n=11)	67% (n=43)	16% (n=10)

Jamison, Huerta, Bishop, & Halladay (under review).

Direction of Clinician Responses: School Age

Criteria / Severity	Less Severe (M<F)	Similar (M=F)	More Severe (F>M)
Social reciprocity	48% (n=30)	48% (n=30)	3% (n=2)
Nonverbal behaviors	44% (n=27)	54% (n=33)	2% (n=1)
Developing, maintaining relationships	25% (n=15)	70% (n=43)	5% (n=3)
Stereotyped/Repetitive Behaviors	55% (n=34)	40% (n=25)	5% (n=3)
Insistence on Sameness	23% (n=14)	73% (n=45)	5% (n=3)
Restricted / Fixated Interests	38% (n=23)	59% (n=36)	3% (n=2)
Hyper-reactivity to Sensory	8% (n=5)	85% (n=52)	5% (n=3)
Hypo-reactivity to Sensory	19% (n=11)	76% (n=43)	7% (n=4)

Jamison, Huerta, Bishop, & Halladay (under review).

Direction of Clinician Responses: Adolescence

Criteria / Severity	Less Severe (M<F)	Similar (M=F)	More Severe (F>M)
Social reciprocity	37% (n=23)	55% (n=34)	8% (n=3)
Nonverbal behaviors	41% (n=25)	56% (n=34)	3% (n=2)
Developing, maintaining relationships	16% (n=10)	69% (n=42)	15% (n=9)
Stereotyped/Repetitive Behaviors	47% (n=29)	48% (n=30)	5% (n=3)
Insistence on Sameness	21% (n=13)	71% (n=44)	8% (n=5)
Restricted / Fixated Interests	31% (n=19)	63% (n=39)	6% (n=4)
Hyper-reactivity to Sensory	8% (n=5)	87% (n=52)	5% (n=3)
Hypo-reactivity to Sensory	23% (n=14)	74% (n=45)	3% (n=2)

Jamison, Huerta, Bishop, & Halladay (under review).

Direction of Clinician Responses: Adult

Criteria / Severity	Less Severe (M<F)	Similar (M=F)	More Severe (F>M)
Reciprocity	31% (n=17)	59% (n=32)	9% (n=5)
Nonverbal behaviors	41% (n=22)	52% (n=28)	7% (n=4)
Developing, maintaining relationships	17% (n=9)	74% (n=39)	9% (n=5)
Stereotyped/Repetitive Behaviors	36% (n=19)	64% (n=34)	0% (n=0)
Insistence on Sameness	19% (n=10)	78% (n=42)	4% (n=2)
Restricted / Fixated Interests	22% (n=12)	76% (n=41)	2% (n=1)
Hyper-reactivity to Sensory	8% (n=4)	87% (n=45)	6% (n=3)
Hypo-reactivity to Sensory	13% (n=7)	80% (n=43)	7% (n=4)

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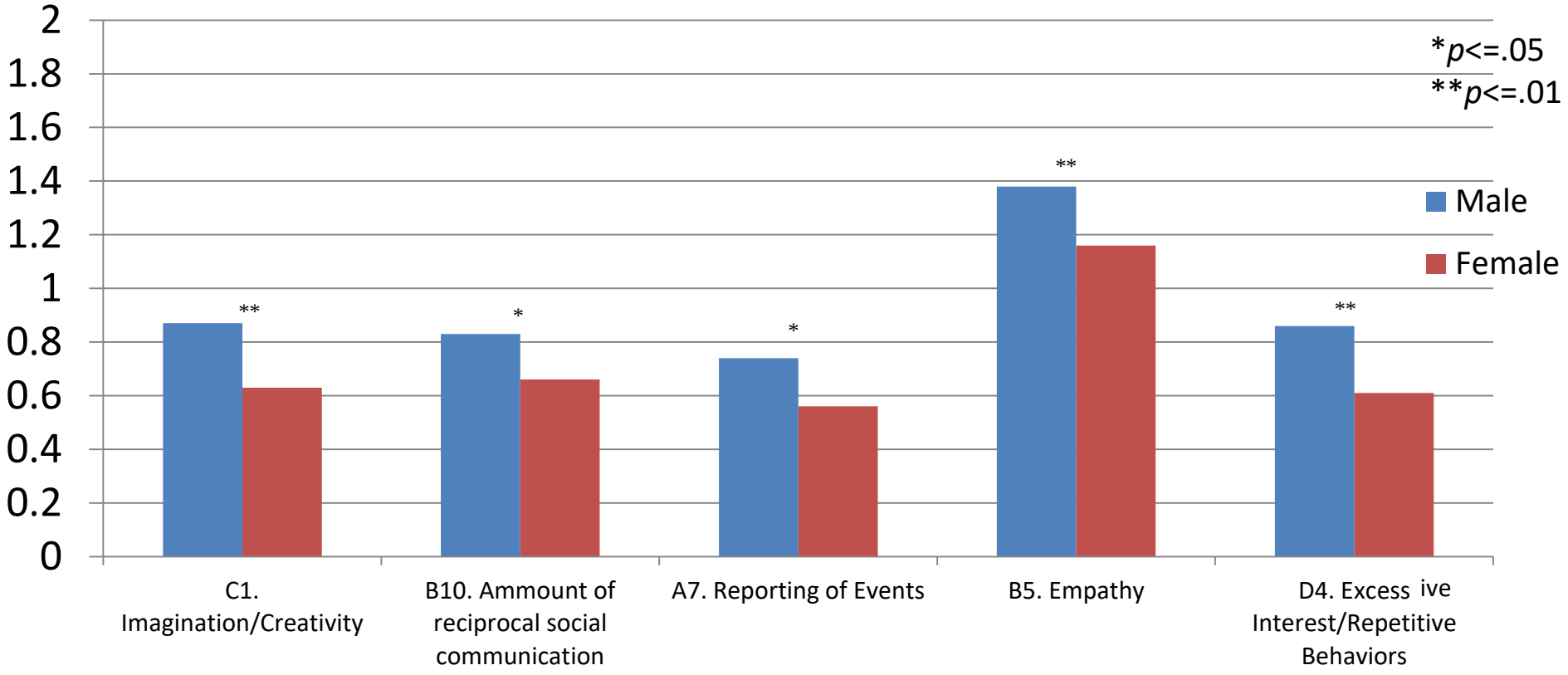
ADOS items showing significant score discrepancies by sex



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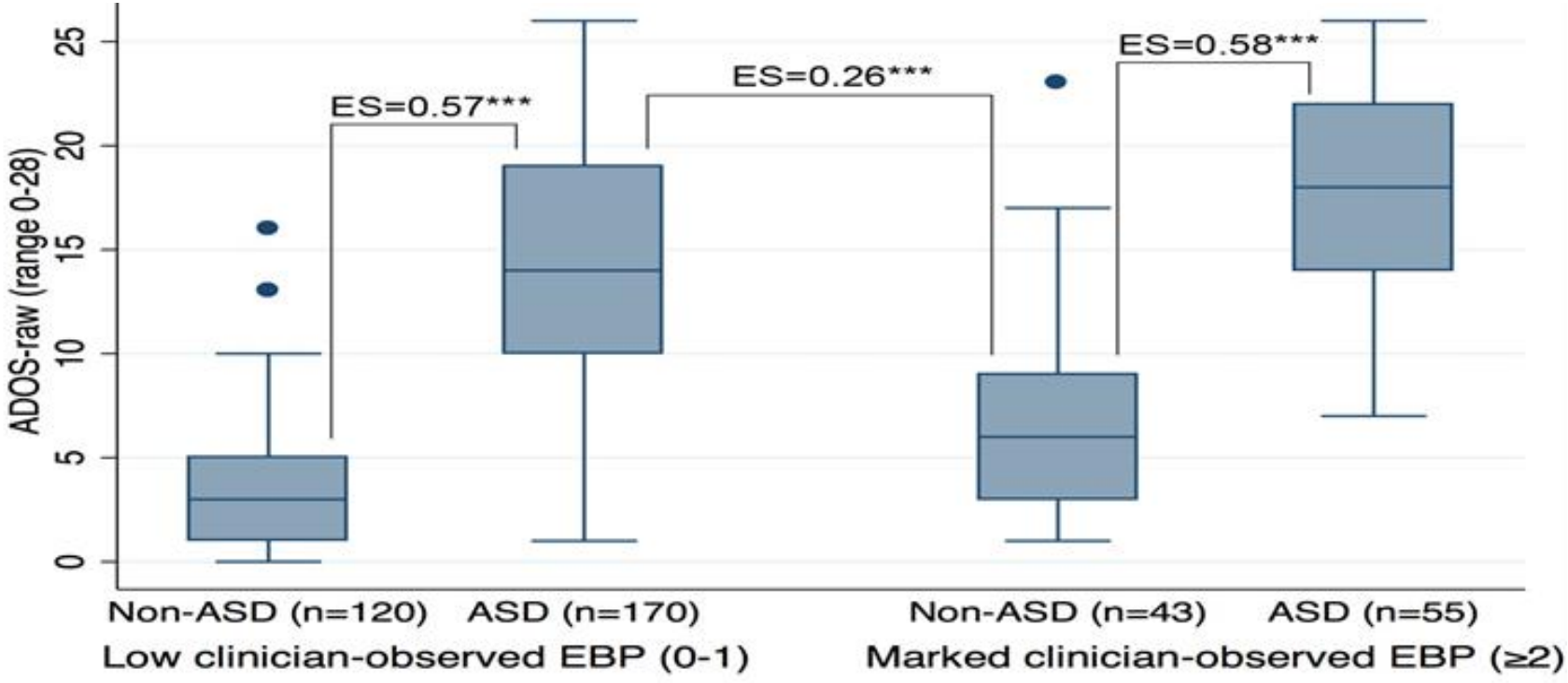

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