Bioavailable testosterone predicts autistic traits in women with and without autism

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AIM

Is bioavailable testosterone predictive of autistic traits in men and women with and without autism?

INTRODUCTION

Fetal testosterone levels predict individual differences in autistic traits, and behaviors related to autism. It is not yet known if testosterone levels in adults are related to autistic traits. Two studies have previously examined autistic traits and testosterone in adults[1,2]. However, these studies used a mix-sex sample and therefore the relationship observed could simply result from sex differences. We therefore completed sex-specific analyses.

METHODS

Participants and Procedures

- Recruited **2 cohorts** of adults with and without autism
- Measured total testosterone and sex hormone binding globulin in serum
- Calculated the **free androgen index (FAI)**
  - $\text{FAI} = \frac{Total\ Testosterone}{Sex\ Hormone\ Binding\ Globulin}$
- Participants took the **Autism Spectrum Quotient (AQ)**

Analysis and Statistics

- Wanted to know whether bioavailable testosterone predicted autistic traits in adults with and without autism.
- Analyzed sexes separately
- Used linear regression, flexible mixture models (women only) , and Bayesian statistics (women only)
- Tried linear regression: when we included diagnosis as a grouping variable in women, we saw a multi-modal distribution of error
- Used flexible mixture model to account for sampling different groups (autism/control) without using diagnosis as a deterministic variable
- However, this leads to model selection bias
- Performed Bayesian inference on a generative model using a probabilistic programming language (e.g. BUGS)
- Uncertainties about the joint distribution of the predictor and outcome variables expressed as probabilities called priors
- Conditioned the model on the data to obtain posterior probabilities that describe the relationship between bioavailable testosterone and autistic traits

RESULTS

Figure 1

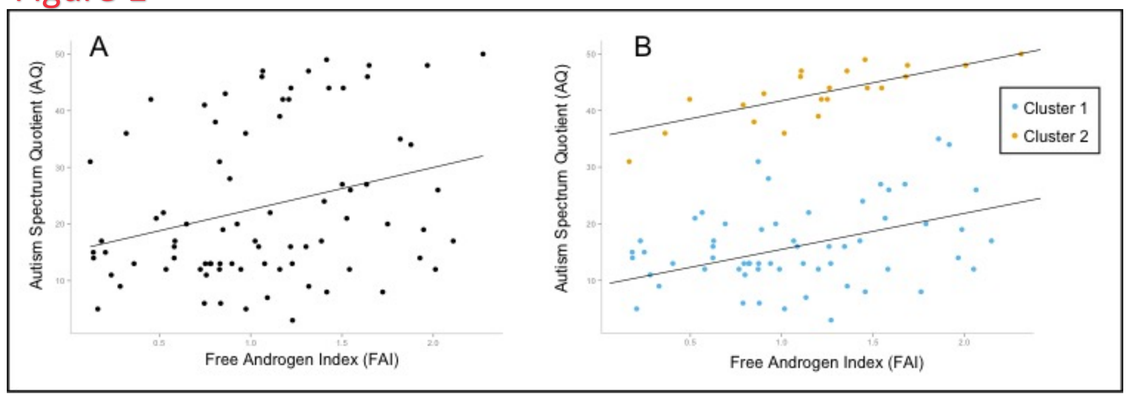

Table 1

	Cohort 1		Cohort 2	
	Females	Males	Females	Males
n	83	81	45	58
ASC / CTR	28 / 55	32 / 49	19 / 26	44 / 14
Age	31.82 ± 7.05	29.88 ± 7.79	31.29 ± 9.75	37.11 ± 13.80
Weight (kg)	67.62 ± 13.13	77.84 ± 12.85	67.91 ± 23.62	80.30 ± 18.72
Height (m)	1.65 ± 0.07	1.79 ± 0.07	169.25 ± 9.06	1.76 ± 0.08
BMI	24.77 ± 5.04	24.36 ± 3.56	23.02 ± 6.00	25.57 ± 5.30
Verbal IQ	111.72 ± 10.46	113.19 ± 11.59	-	-
Performance IQ	109.88 ± 12.88	112.15 ± 11.96	-	-
Total IQ	112.22 ± 11.13	114.47 ± 11.76	-	-
Follicular / Ovulatory / Luteal	25 / 8 /43	-	8 / 5 / 12	-
HC / no HC	22 / 57	-	6 / 38	-

Figure 2

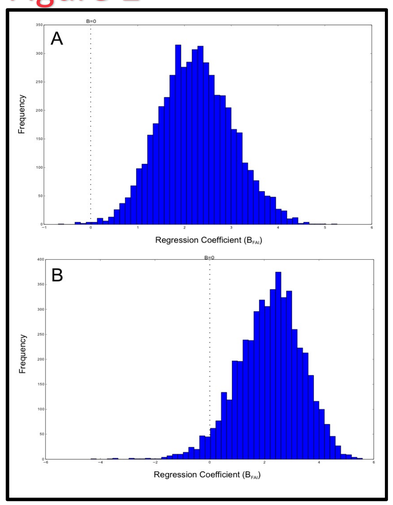

Table 2

	regression coefficient		regression coefficient variation		intercept		latent clusters	predicted variable	
Model 1 distribution	uniform continuous		-		uniform continuous		chinese restaurant process	normal distribution	
parameter	min	max	-		min	max	α	μ	σ
parameter value	-10	10	-		-200	200	0.3, [0.033, 0.1, 0.3, 0.9, 2.7, 8.1, 24.3]	Model 1 likelihood function	uniform continuous [0.1-10]
Model 2	uniform continuous		uniform continuous		uniform continuous		chinese restaurant process	normal distribution	
	min	max	min	max	min	max	α	μ	σ
	-10	10	-1	1	-200	200	uniform continuous [0.1-20]	Model 2 likelihood function	uniform continuous [0.1-10], memoized on cluster

Table 3

		Cohort 1				Cohort 2			
		Model 1 ($\alpha = 0.3$)		Model 1 ($\alpha = 0.3$)		Model 2 (α uniform continuous)	
		prior	posterior	prior	posterior	prior	posterior
latent clusters	ESS		1211		3031		3370
	probability > 1	0.7578	>0.999	0.7064	0.996	0.9922	>0.999
	95% HDI		[2, 3]		[2, 3]		[2, 5]
	90% HDI		[2, 3]		[2, 3]		[2, 5]
	80% HDI		[2, 2]		[2, 2]		[2, 4]
	70% HDI		[2, 2]		[2, 2]		[3, 4]
	50% HDI		[2, 2]		[2, 2]		[2, 3]
	25% HDI		[2, 2]		[2, 2]		[3, 3]
regression coefficient	ESS		713		849		543
	probability > 0	0.499	0.998	0.497	0.745	0.511	0.962
	95% HDI		[0.767, 3.863]		[-2.864, 3.701]		[-0.063, 4.428]
	90% HDI		[0.865, 3.477]		[-1.825, 3.439]		[0.385, 4.139]
	80% HDI		[1.175, 3.205]		[-0.696, 3.129]		[0.843, 3.766]
	70% HDI		[1.355, 2.964]		[-0.304, 2.676]		[1.173, 3.563]
	50% HDI		[1.661, 2.721]		[0.203, 2.016]		[1.564, 3.110]
	25% HDI		[1.884, 2.371]		[0.562, 1.371]		[2.255, 2.967]

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RESULTS

Main Result

- **No relationship** between bioavailable testosterone and autistic traits in **men**
- **Positive relationship** between bioavailable testosterone and autistic traits in **women**
- Both findings **replicated** in Cohort 2

Figure 1: Free androgen index positively predicts AQ in women. Plot A shows the line of best fit that is obtained if the sample is treated as a single group. Plot B shows the result of a finite mixture model where $k = 2$. Two groups are recovered; the regression coefficient is equal between groups, and closely matches the regression coefficient obtained from the entire sample.

Table 1: Descriptive statistics for Cohorts 1 & 2

Table 2: Priors for generative models 1 and 2

Figure 2: Posterior distribution of regression coefficient in females in Cohort 1 (A) and Cohort 2 (B)

Table 3: Posteriors for generative models for Cohorts 1 and 2

Finer Details

Flexible mixture model segregated participants roughly back to ASC/control, but about 10% were sorted to opposite group. Bayesian analysis suggested 2-3 clusters in Cohort 1 and 2-5 clusters in Cohort 2. These clusters were highly stable (we calculated a co-occurrence matrix). Results suggest AQ not normally distributed at small sample size and diagnosis may not always perfectly map to autistic traits (diagnosis is subjective).

DISCUSSION

- Relationship between AQ and bioavailable testosterone in women could either be due to **direct effect** of testosterone on cognition in adulthood or to **indirect effect** of fetal testosterone on both endocrine system and brain
- Most likely a mixture of both; can't tell from this study
- Autism liability (determining autism diagnosis) and autistic traits are separate constructs.[3]

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