

# Sex Differences in Age of Illness Onset of Treatment-Resistant Psychosis

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## INTRODUCTION

Within schizophrenia, age of illness onset (AIO) is influenced by sex, with males typically experiencing younger AIO than females<sup>1,2</sup>. Females also exhibit two age onset peaks, one in their 20s and another in their 40s<sup>3,4</sup>. This delayed onset among females is possibly due to estrogen's antidopaminergic effects<sup>5-7</sup>. However, the patterns of sex-related AIO in the subset of patients with treatment-resistant psychosis (TRP), and more specifically treatment-resistant schizophrenia (TRS), are unknown. Given that TRS may involve less dopaminergic pathology than schizophrenia<sup>8,9</sup>, its response to estrogen's protective effects might be less evident. Therefore, we hypothesized that in TRP and TRS, both sexes would: a) exhibit similar AIO, and b) demonstrate a unimodal distribution of AIO.

## METHODOLOGY

- 465 patient profiles from the BC Psychosis Program were reviewed
  - 218 patients were identified as TRS, meeting the following inclusion criteria: schizophrenia diagnosis, history of Clozapine use, either 2+ PANSS Positive items scored  $\geq 4$  at admission or 1+ items scored  $\geq 6$ , and a SOFAS\* score at admission  $\leq 60$
  - Patients were further divided by sex
  - AIO was determined by the age at first admission
- Independent t-tests conducted to compare AIOs  
→ Exploratory analysis of sex-based onset distribution patterns

\*Social and Occupational Functioning Assessment Scale

## RESULTS

- Average AIO was 23.5 (8.6) years in TRP, and 22.4 (7.0) years in TRS
  - Peak age was 18.0 years, approximately 6.5-7.5 years younger than that of published schizophrenia samples<sup>10</sup>
  - Males have a younger AIO than females
- AIO distribution:**
- Males → sharply peaked unimodal left-skewed distribution
  - Females → weakly bimodal left-skewed distribution; flatter first peak compared to males

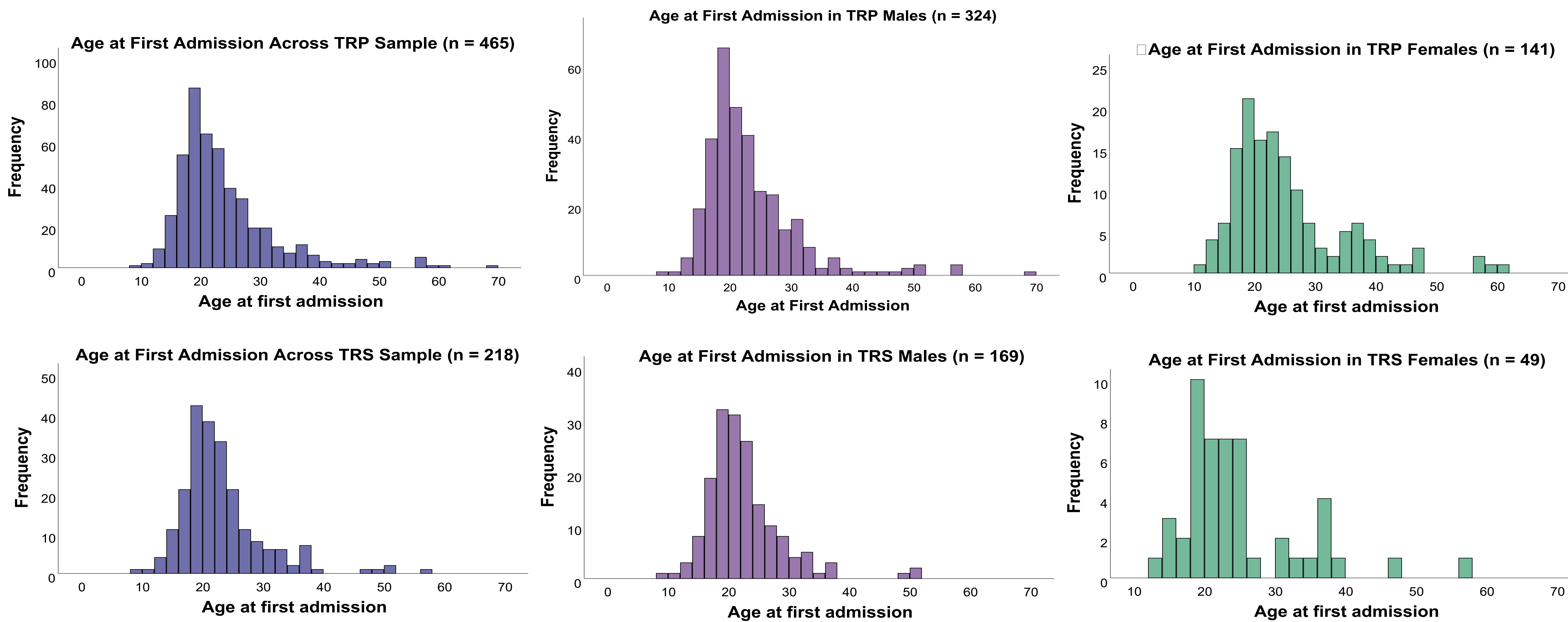
Table 1: Demographics and Sample Characteristics

	TRP (N = 465)			TRS (N = 218)		
	Female (n = 141) M (SD)	Male (n = 324) M (SD)	p-value	Female (n = 49) M (SD)	Male (n = 169) M (SD)	p-value
Age (years)	41.60 (13.79)	36.59 (12.98)	<.001	41.96 (13.09)	36.98 (12.19)	0.014
Education (years)	12.05 (2.35)	11.33 (2.01)	<.001	12.00 (2.41)	11.09 (1.91)	0.007
Duration of illness (years)	16.89 (12.02)	13.84 (11.30)	0.009	17.69 (11.57)	15.19 (11.86)	0.192
Duration of BCPP Hospitalisation (days)	179.33 (93.94)	173.35 (89.06)	0.516	183.24 (68.21)	183.57 (76.47)	0.979
<b>PANSS</b>						
Positive symptoms	23.02 (7.31)	22.11 (6.37)	0.170	25.06 (6.06)	24.21 (5.31)	0.338
Negative symptoms	18.79 (7.54)	22.06 (7.31)	<.001	20.76 (6.85)	23.61 (7.25)	0.015
Disorganization	28.26 (6.58)	29.60 (7.33)	0.072	29.27 (5.89)	31.34 (6.82)	0.055
Excitement	11.78 (5.16)	9.88 (4.65)	<.001	12.22 (5.40)	10.49 (5.01)	0.037
Emotional distress	11.40 (3.83)	10.11 (3.90)	0.002	12.08 (3.54)	10.27 (3.91)	0.004
Total	93.25 (20.39)	93.76 (18.81)	0.800	99.39 (19.28)	99.92 (17.56)	0.856
<b>RAPP</b>						
Basic needs	3.99 (2.65)	3.26 (2.02)	0.002	3.87 (2.86)	3.24 (2.14)	0.101
Psychopathology	9.41 (4.26)	8.65 (4.14)	0.083	9.91 (4.23)	9.44 (4.06)	0.484
Life skills	6.22 (4.34)	5.74 (3.80)	0.242	6.62 (4.40)	6.44 (3.90)	0.789
Total	19.63 (9.49)	17.65 (8.20)	0.028	20.40 (9.63)	19.12 (8.37)	0.371
<b>Ethnicity</b>						
	N (%)	N (%)	X <sup>2</sup> p-value	N (%)	N (%)	X <sup>2</sup> p-value
Caucasian	95 (67.4%)	227 (70.1%)	0.564	33 (67.3%)	121 (71.6%)	0.565
Non-Caucasian	46 (32.6%)	97 (29.9%)		16 (32.7%)	48 (28.4%)	
<b>Primary Diagnosis</b>						
Schizophrenia	68 (48.2%)	224 (69.1%)	-	-	-	-
Schizoaffective disorder	45 (31.9%)	73 (22.5%)	<.001	-	-	-
Mood disorder with psychosis	14 (9.9%)	5 (1.5%)		-	-	-
Other	14 (9.9%)	22 (6.8%)		-	-	-
Substance use disorder	74 (52.5%)	212 (65.4%)	0.008	27 (55.1%)	111 (65.7%)	0.176

PANSS = Positive and Negative Symptoms Scale; RAPP = Routine Assessment of Patient Progress

Table 2: Average Age of Illness Onset, By Sex

	Peak	Median	IQR	Mean	p-value
<b>TRP</b>					
Total sample	18.0	21.0	18.0 – 26.0	23.46 (8.56)	
Male	18.0	21.0	18.0 – 26.0	22.80 (7.95)	0.011
Female	18.0	22.0	18.0 – 28.0	24.98 (9.68)	
<b>TRS</b>					
Total sample	18.0	21.0	18.0 – 24.0	22.43 (7.00)	
Male	18.0	21.0	18.0 – 24.0	21.90 (6.35)	0.037
Female	18.0	22.0	18.5 – 25.5	24.27 (8.69)	



**CONCLUSIONS** The sex-onset patterns in TRP and TRS reflect those observed in schizophrenia, where males experience illness onset at a younger age than females. However, our findings also suggest that TRP and TRS may represent distinct, more extreme subtypes with earlier onset overall. A Meltzer et al. (1997) study also found TRS AIO to be earlier than that in schizophrenia, consistent with our findings, but it did not find significant sex-differences within TRS<sup>11</sup>. Within TRP and TRS, sex-onset differences suggest that treatment resistance encompasses a heterogeneous group, likely exhibiting variations in illness course and functioning outcomes.

**LIMITATIONS** One limitation lies in the conflation of sex and gender. Future research should aim to clarify the interplay between sex and gender-related factors in schizophrenia. Additionally, the study's reliance on a convenience sample may not be representative of the broader TRP/TRS populations.

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