

# Transdiagnostic Predictors of Early Clinical Trial Dropout Among Youth With Mental Illness: A Pooled Secondary Analysis of Three Adherence-Promotion Trials

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## Methodological Issue Being Addressed

Youth with serious mental illness are at high risk for early dropout from clinical trials, compromising statistical power, threatening internal validity, and obscuring interpretation of treatment effects. Identifying reliable transdiagnostic predictors of dropout is essential for improving trial design, participant engagement, and retention strategies. This secondary analysis examines predictors of early discontinuation across three prospective adherence-promotion trials, addressing a key methodological challenge in youth mental health research: retaining high-risk participants long enough to evaluate intervention efficacy.

## Introduction

Adolescence and young adulthood are the periods of greatest risk for the onset of many serious mental illnesses, bipolar disorder key among them. Although neurodevelopmental disorders, such as ADHD typically begin in childhood, they often persist into adolescence and early adulthood continuing to impair functioning and complicating clinical trial participation. Across these conditions, adolescents and young adults face substantial challenges that can interfere with sustained trial engagement, including developmental transitions, symptom burden, and structural barriers.

Retention difficulties in youth mental health trials reduce statistical power, limit the ability to detect intervention effects, and can bias conclusions. Prior work has suggested that demographic factors, clinical severity, and treatment complexity may influence dropout, but findings have been inconsistent. This pooled analysis examines transdiagnostic predictors of discontinuation across three adherence-promotion trials. We predicted that younger age, male sex, non-White race, greater number of prescribed medications, worse medication adherence at baseline, and higher disease severity would predict higher dropout. By integrating data across disorders with differing developmental onset patterns, this study aims to clarify which participant characteristics truly place youth at risk for dropping out of clinical research.

## Methods

A pooled sample (N = 71) of 3 prospective clinical trials testing a common adherence promotion intervention modified for the disease of interest were analyzed to evaluate factors that related to drop out in participants age 13-26. The IGNITE trial (bipolar disorder) included 6-months of follow-up, CAE-ADHD was a 12-week intervention study, and CAE-E (bipolar disorder) measured primary outcomes at 6 months and followed participants for 12 months. Variables related to clinical trial drop out were assessed for this secondary analysis through 6 months. Dropout was defined as discontinuation of study participation before completing all scheduled study visits and follow-up assessments. Participants were classified as dropouts if they voluntarily withdrew, were lost to follow-up, or otherwise stopped participating prior to study completion. We evaluated clinical (diagnosis, disease severity, number of prescribed medications, medication attitudes, medication adherence [poor adherence was defined as missing more than 20% of prescribed medication doses]) and demographic (sex, age, race/ethnicity) variables in relation to drop out. See Figure 1 for an example of intervention materials for IGNTIE

Figure 1: Intervention Module Schedule for Customized Adherence Enhancement (CAE)

Session	Modules
Session 1	Psychoeducation
Session 2	Communication with parents, peers, clinicians
Session 3	Medication Routines
Session 4	Modified Motivational Enhancement Therapy (MET) for Risk Taking Behavior
Session 5	Booster; Reinforcement/additional skill-building, planning for success!

## Results

Mean sample age was 20.21 (2.67), 53 (74.6%) female, 18 (25.4%) non-White with diagnoses of BD (n = 56, 78.9%) and ADHD (n = 15, 21.1%). Interventions tested included customized adherence engagement (CAE) tailored to the specific mental health disorder, see Figure 2 for participant distribution. Among the dropouts (n = 21, 29.6%), most (n = 17, 81%) of the drop-outs occurred at the < 12-week time-point. Age, race, biologic sex, and disease severity were not statistically significantly associated with drop out, see table 1. Variables that were statistically significantly associated with drop out were less education (in years, p=0.037) and fewer prescribed medications (p=0.021), see figures 3, 4.

Figure 2: Distribution of Participants per Intervention Type (N = 71)

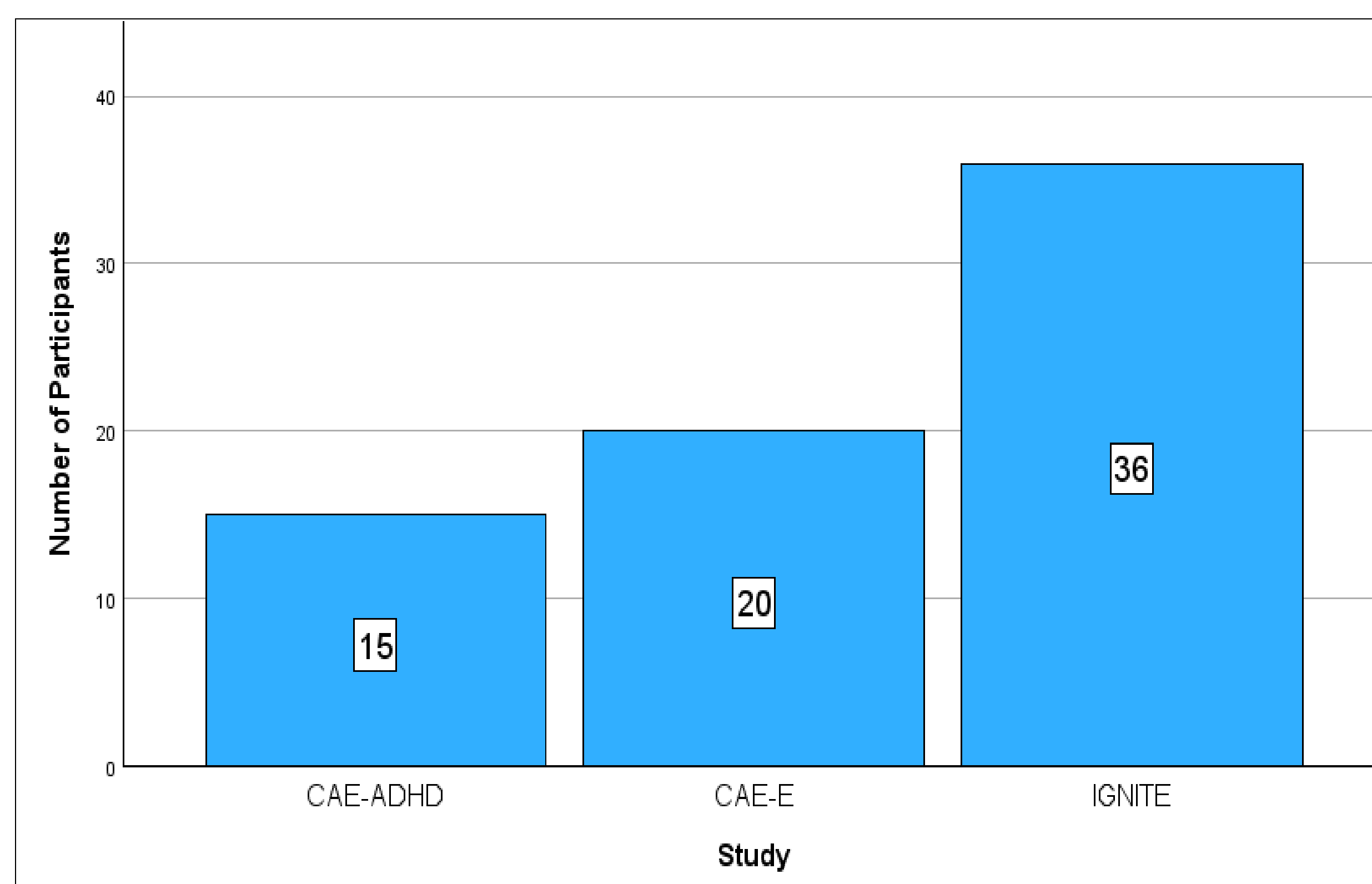


Table 1: Demographic and Clinical Characteristics Based on Attendance (N = 71)

Variables	All Participants (N = 71)		Participants Who Completed the Study (n = 50)		Participants Who Dropped Out (n = 21)		p-value
	N	%   M (SD), Range	N	%   M (SD), Range	N	%   M (SD), Range	
Age	71	20.21 (2.67), 13 – 26	50	20.60 (2.56), 15 – 26	21	19.29 (2.78), 13 – 24	.18
Biological Sex							
Female	53	(74.6%)	39	(78.0%)	14	(66.7%)	.38
Male	18	(25.4%)	11	(22.0%)	7	(33.3%)	
Race							
White	53	(74.6%)	38	(76.0%)	15	(71.4%)	.77
Non-White	18	(25.4%)	12	(24.0%)	6	(28.6%)	
Education (in years)	71	12.79 (1.91), 7 – 18	50	13.12 (1.70), 9 – 18	21	12.00 (2.19), 7 – 16	.037
Disorder							
Bipolar Disorder	56	(78.9%)	39	(78.0%)	17	(81.0%)	1.00
ADHD	15	(21.1%)	11	(22.0%)	4	(19.0%)	
Number of Prescribed Medications	71	1.49 (0.65), 1 – 3	50	1.60 (0.67), 1 – 3	21	1.24 (0.54), 1 – 3	.021
Medication Adherence (Past Week)	71	29.48 (31.40), 0 – 100	50	30.14 (31.31), 0 – 100	21	27.89 (32.33), 0 – 100	.71
Medication Adherence (Past Month)	70	25.66 (24.32), 0 – 100	49	25.57 (24.12), 0 – 100	21	25.87 (25.36), 0 – 83.33	.81
YMRS Total Score	56	7.11 (6.83), 0 – 31	39	6.87 (6.59), 0 – 31	17	7.65 (7.55), 0 – 29	.82
GAF Total Score	20	59.95 (11.71), 41 – 89	16	59.75 (11.82), 41 – 89	4	60.75 (12.97), 49 – 79	.93
CGI							
Mania	56	1.86 (1.03), 1 – 5	39	1.82 (1.10), 1 – 5	17	1.94 (0.90), 1 – 4	.37
Depression	56	2.57 (1.40), 1 – 6	39	2.51 (1.49), 1 – 6	17	2.71 (1.21), 1 – 5	.44
Overall	56	2.75 (1.37), 1 – 6	39	2.67 (1.46), 1 – 6	17	2.94 (1.14), 1 – 5	.35
AMSQ Total Score	52	7.37 (3.57), 2 – 17	35	6.91 (3.48), 2 – 15	17	8.29 (3.69), 4 – 17	.18
ADHD RS-5							
Inattention	15	15.60 (4.70), 5 – 22	11	15.73 (5.12), 5 – 22	4	15.25 (3.95), 12 – 20	.65
Hyperactivity	15	13.53 (4.07), 6 – 22	11	13.91 (4.30), 6 – 22	4	12.50 (3.70), 7 – 15	.95
Total Score	15	29.13 (7.67), 17 – 43	11	29.63 (8.61), 17 – 43	4	27.75 (4.92), 24 – 35	.60

a\*\*\* A higher score (percentage) on the TRQ indicates a greater percentage of missed medications. 0 = No missed medications. 100 = Missed all medications.  
 A higher score on the YMRS indicates more severe mania.  
 A higher score on the GAF indicates higher levels of functioning.  
 A higher score on the CGI-BP subscales indicates a more severe illness.  
 A higher score on the AMSQ indicates a worse attitude toward medication.  
 A higher score on the ADHD RS-5 indicates greater symptom severity.

Figure 3: Education in Years by Attendance Groups

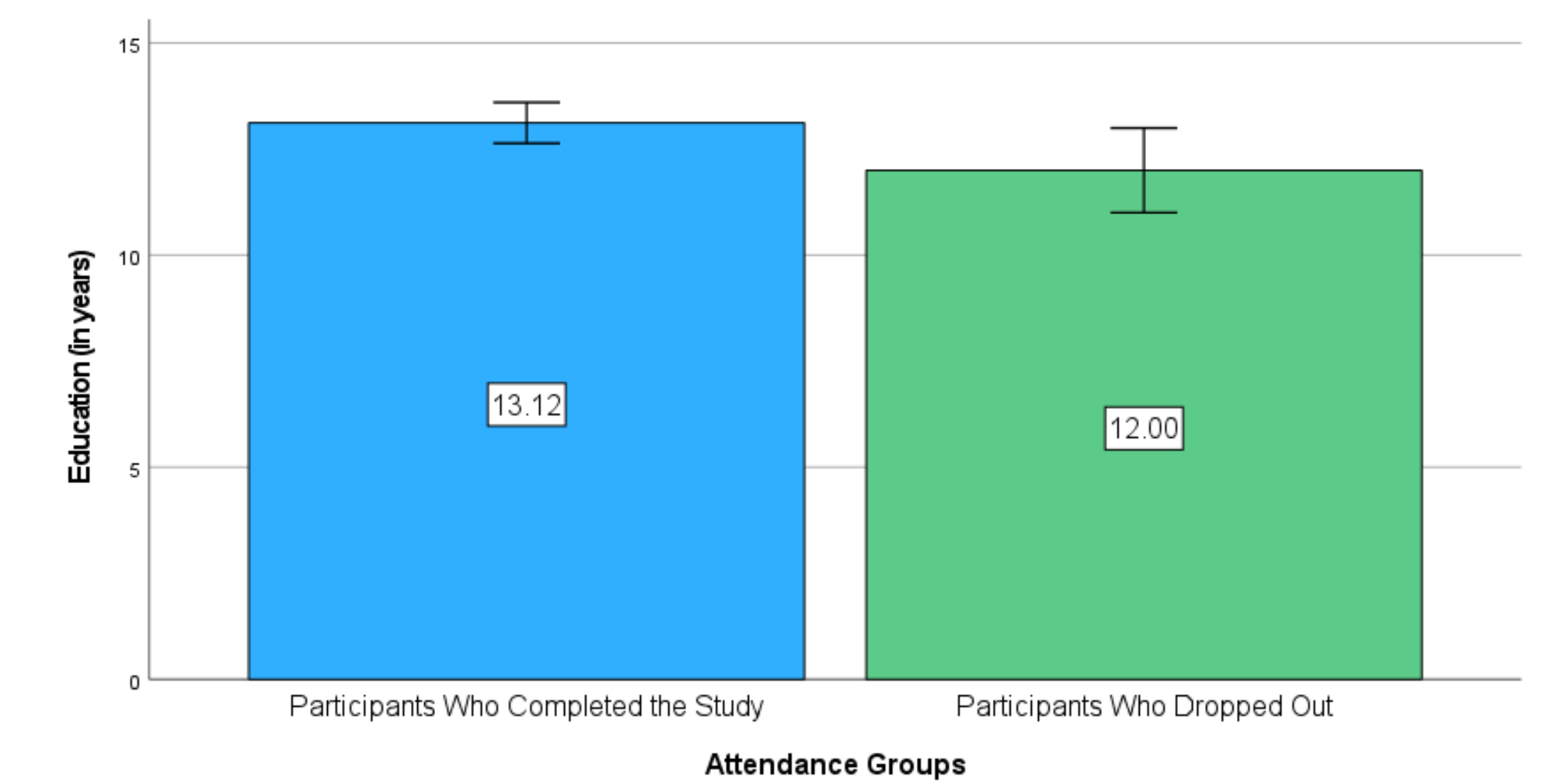
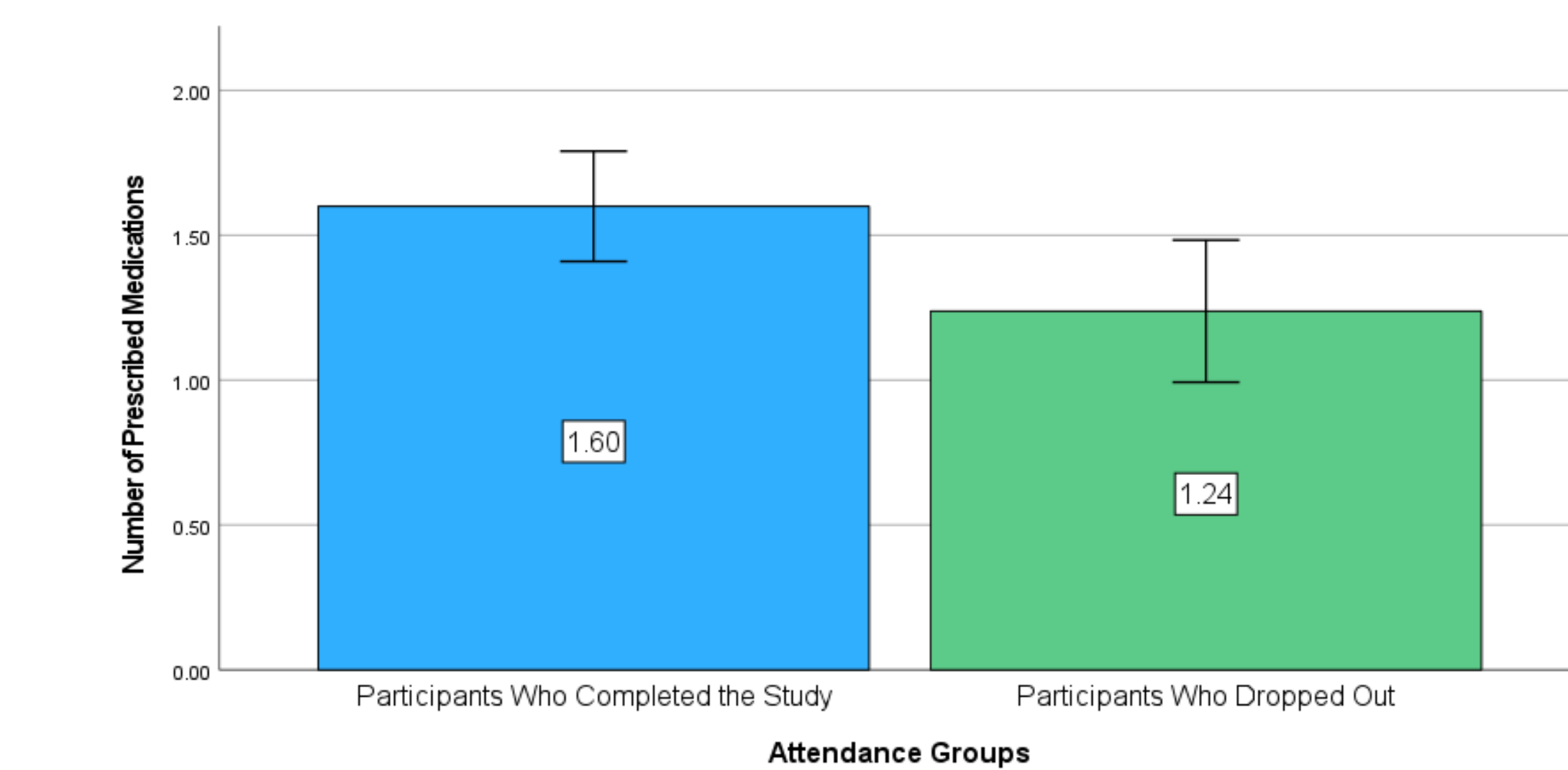


Figure 4: Number of Prescribed Medications by Attendance Groups



## Conclusions

- Lower educational attainment was a strong predictor of early dropout
- Age, sex, race, diagnosis, illness severity, and baseline adherence were not associated with discontinuation
- Most dropout occurred within the first 12 weeks, identifying **early study engagement as the highest-yield target** for retention efforts in AYA trials
- These findings suggest that AYA trial attrition is driven more by modifiable communication and design factors than by clinical severity.
- **Implications for clinical trials:**
  - Align consent and study materials with the literacy level of AYA participants.
  - Use visual and graphic-based materials to support comprehension.
  - Implement front-loaded engagement strategies during early visits.
- Given the high per-participant cost of clinical trials, small gains in early retention can produce meaningful cost savings.