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Gender differences in outcomes of early intervention services for first episode psychosis

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Abstract

Aims: There is growing interest in early intervention in psychotic disorders. However, gender differences in the outcomes of such treatment have not been studied in a randomized clinical trial.

Methods: Patients diagnosed with schizophrenia spectrum disorders with less than 6 months antipsychotic exposure entered a cluster randomized trial of early intervention services compared to usual care in the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) study. Masked evaluators assessed the Quality of Life Scale (QLS) and the Positive and Negative Syndrome Scale (PANSS) every 6 months. Our secondary analyses examined gender differences in baseline characteristics, 2-year gender outcomes, and intervention responses.

Results: Altogether 404 individuals aged 15–40 entered the study: 111 (27.4%) women and 293 (72.5%) men. At baseline, women were significantly more likely to have been married ($p = .007$) and to be living independently ($p = .012$) than men. Women were also more likely to be diagnosed with schizoaffective disorder, bipolar type ($p = .006$) and scored higher on the depression subscale of the PANSS ($p = .0004$) but not the CDSS. Women were less likely to use or abuse cannabis ($p = .0004$), though no less likely to abuse alcohol. Controlling for these differences, there were no significant gender differences in the QLS or PANSS outcomes.

Conclusion: Baseline gender differences in comorbid substance use and prevalence of mood symptoms in women with first episode psychosis are consistent with previous studies. The absence of significant gender differences in outcomes with early intervention has not been previously reported in a multi-site randomized US clinical trial.

KEYWORDS
coordinated specialty care, early intervention, gender outcomes, schizophrenia

1 | INTRODUCTION

There is increasing interest in biological and psychosocial differences between women and men in the clinical presentation, course of illness, and treatment outcomes of mental disorders and specifically in psychotic disorders such as schizophrenia (Riecher-Rössler, 2017). These concerns reflect a broader concern that sex and gender influences on health have been long neglected throughout medicine (Thande et al., 2019). Recent studies suggest that women with psychotic disorders are more likely to present with positive and affective symptoms while men have more prominent negative symptoms and cognitive impairments (Comacchio et al., 2020; Heitz et al., 2019; Irving et al., 2021), and are more likely to meet criteria for comorbid substance use disorders (Irving et al., 2021). Female patients have been

found to experience a pre-psychotic prodrome for twice as long as male patients (Seeman, 2018), and experience full psychotic disorders at later age (Seeman, 2019). Women have also been reported to experience less impaired social functioning than men (Dubreucq et al., 2021) and it has been suggested that women respond more quickly and completely to available treatments (Seeman, 2019). While short-term studies suggest better quality of life among women with psychotic disorders than men (Dubreucq et al., 2021), longer term studies suggest these differences dissipate over time (Thara & Kamath, 2015).

Among the most important recent developments in the treatment of schizophrenia has been growing evidence that early intervention services (IES), known as Coordinated Specialty Care in the United States (Heinssen et al., 2022) can have important positive impact on outcomes on when provided early in course of the illness (Correll et al., 2018). Several studies have focused specifically on differences between women and men in their first episode of psychosis (FEP). One study from Switzerland (Heitz et al., 2019) and another from Italy (Comacchio et al., 2020) found that women presented with higher levels of affective symptoms, greater insight into their illness, and higher levels of functioning than men, who showed more severe negative symptoms.

Data from 1098 Early Intervention Service patients in London showed men with early psychosis were more violent than women at both admission and 1-year follow up while women had more suicide attempts at admission and more psychiatric hospitalization at follow-up (Tseliou et al., 2017). Another London study of 3350 first episode patients showed significant differences between sexes in on 21 symptoms identified through natural language processing of electronic health records. The study concluded that men had more negative symptoms and women had more depressive and manic symptoms (Irving et al., 2021). Finally, in a major longitudinal study, 5 years of data from 578 participants in the Danish OPUS randomized trial of intensive early psychosis treatment (Thorup et al., 2014) were used to compare men and women at 2- and 5-year follow-up assessments. However differences between men and women in the impact of treatment were not examined (Thorup et al., 2014). As in previous studies, males consistently had more severe negative symptoms, were more likely to live alone, and had more problems with substance abuse while women achieved higher levels of social functioning at follow-up and were more likely to reach a state of recovery.

To our knowledge, no study has evaluated gender differences in service use and outcomes between treatment groups in a randomized clinical trial of Coordinated Specialty Care for early psychosis. The recent National Institute of Mental Health (NIMH)-funded study called Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) was a 34-site cluster randomized trial of 404 patients with FEP performed in community clinics. The coordinated specialty care intervention was called NAVIGATE to indicate that it was designed to help clients find their way to comprehensive services and ultimately to recovery. In the RAISE-ETP study, NAVIGATE improved quality of life, reduced symptoms (Kane et al., 2016) and increased school and work involvement (Rosenheck et al., 2017) as compared to usual community care. Interaction analyses have shown greater improvement in those with shorter duration of untreated psychosis (Kane et al., 2016) or higher socio-economic status (Bennett & Rosenheck, 2020). However, a secondary analysis comparing the response of men and women to treatment has yet to be conducted. In this paper, we use data available from the RAISE-ETP trial, to compare women and men on baseline characteristics, 2-year outcomes and use of services, and differential response to NAVIGATE or usual care. Since available studies suggests that women have better baseline functioning and quality of life, greater insight than men we hypothesized they would benefit more than men from NAVIGATE compared to usual care.

2 | METHODS

Previous publications have included details on the recruitment process including a CONSORT diagram of recruitment and disposition (Kane et al., 2016), and a detailed description of NAVIGATE (Mueser et al., 2015).

2.1 | Subjects and sites

Inclusion criteria included: presenting for first episode of psychosis (schizophrenia, schizoaffective bipolar disorder, schizoaffective depressive disorder, Schizophreniform provisional or definite, or brief psychotic disorder), and exposure to antipsychotic medication for fewer than 6 months. Enrollment occurred between July 2010 and July 2012. Written informed consent was obtained from adult participants or from legal guardians for those under 18 years old. The Institutional Review Boards of the coordinating centre and at each site approved the study. A NIMH Data and Safety Monitoring Board provided oversight to the original study. Thirty-four community mental health treatment centres across the United States were randomized to provide either NAVIGATE or to usual community care. The Clinical Trials.gov number for the original study was NCT01321177.

2.2 | Intervention

NAVIGATE included: (a) a web-based decision support system for assisting personalized medication management called COMPASS; (b) family psycho-education; (c) individual, resilience-focused training in illness self-management; and (d) supported employment and education via remote training and consultation (Mueser et al., 2015). Participants without initial interest in work or school received continuing encouragement to participate in supported employment and education.

2.3 | Assessments

Masked evaluators remotely assessed quality of life and symptoms (see measures, below) at baseline and every 6 months for 2 years via

secure videoconferencing. Additional self-report assessments were obtained by local research assistants at each site.

Self-report data on socio-demographic characteristics were recorded at baseline. Interviews measured service use and employment on a monthly basis.

2.4 | Measures

Initial assessment included documentation of socio-demographic characteristics. A central team of blinded evaluators assessed quality of life using the Quality of Life Scale (QLS) (Heinrichs et al., 1984) with four subscales of interpersonal relationships, instrumental role functioning, intrapsychic foundations (more recently re-conceptualized as 'motivation'), and common objects and activities used in daily life. Psychiatric symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) with five subscales (Wallwork et al., 2012); depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington & Maticka-Tyndale, 1993).

Patients self-reported well-being was assessed using a reduced versions of the perceived well-being scale (Ryff, 1989), the Mental Health Recovery Measure (Young & Bullock, 2003), the Autonomy Support Scale-Short Form (Williams et al., 1998), the Brief Evaluation of Medication Influences and Beliefs (Dolderk et al., 2004), and the Stigma Scale (King et al., 2007).

2.5 | Statistical methods

Baseline characteristics were compared between genders using linear regression with interactions between round dummies and gender.

All standard errors in the longitudinal regressions were clustered by site to account for arbitrary error correlations within a site, including across individuals over time. All regressions also controlled for baseline marital status, current residence, diagnosis, cannabis use, previous hospitalizations, age, and baseline depression symptoms because these variables were shown to be imbalanced by gender at baseline.

Longitudinal analyses of gender differences included terms representing gender, time in months since the baseline (a single continuous variable) and the interaction of gender by time.

Longitudinal analyses of gender differences in treatment effects included main effects for gender, time, and treatment; the interaction of gender by time and treatment by time; and the term of interest, the three-way interaction of gender by time by treatment. Subscales were examined only for the primary outcome, the QLS, to limit artifactual results from multiple comparisons.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 presents the demographic comparison of men and women at study entry. A total of 111 (27.4%) women participants and 293 (72.5%) men participants were included in the study. Mean age of women was significantly older at 24.33 ± 6.19 years compared to 22.68 ± 4.5 years of male patients ($p = .0067$). Eighty-nine (80.2%) of women were never married, compared to 269 (91.8%) of men ($p = .007$). A total of 31 (27.9%) of women lived independently and 72 (64.9%) lived with family members including parents, grandparents, and siblings. In comparison, only 41 (14.0%) of male patients lived independently and 215 (73.4%) lived with family. Women were significantly more likely to have been married ($p = .007$) and significantly more likely to be living independently ($p = .012$) compared to male patients. A total of 44 (40%) of women were covered by public insurance compared to 83 (28.5%) of men ($p = .03$).

There were no significant gender differences in race/ethnicity, patient education and employment status, or parental education.

In diagnosis, a great proportion of women than men (14 women, 12.6% and 10 [3.4%] men) were diagnosed with schizoaffective disorder, bipolar type ($p = .006$).

Turning to substance abuse or dependence, women were overall less likely to use or abuse drugs of any type with 24 (28.8%) meeting abuse or dependence criteria for lifetime cannabis use, compared to 116 (39.6%) male patients ($p = .002$). There were no significant gender differences in lifetime alcohol abuse or dependence. Recent use of illegal drugs including cannabis also was significantly different across genders with women reporting drug use (mean 1.55 ± 5.33 days) of the 30 days prior to enrollment, significantly fewer days than men (mean 3.74 ± 8.07 days) ($p = .008$).

There were no significant gender differences the proportions with one or more hospitalizations prior to study enrollment, on measures of medication compliance or on either the duration of untreated psychosis or the percentage of subjects above the median duration of untreated psychosis (Table 3).

On the Heinrich Carpenter measure of Quality of Life Interview women scored significantly higher than men ($p = .02$) (Table 2). Specifically, women averaged higher on on the interpersonal relations and the common objects and activities subscales (Table 2). There were no differences within the instrumental role subscale and intrapsychic foundations subscale.

On the PANSS symptom severity scale, women scored significantly higher ($p = .0004$) on the depression subscale (Table 3). There were no significant gender differences on the total PANSS score or on other subscales of the PANSS (positive, negative, disorganized/concrete, and excited). There were also no significant differences in CDSS, a specific depression symptom severity scale.

There were no further gender differences in any self-reported social and well-being measures including the perceived Well-being Scale, the Mental Health Recovery Measure, the Autonomy Support Scale-Short Form, the Brief Evaluation of Medication Influences and Beliefs score, and the Stigma Scale score.

3.2 | Longitudinal analyses

Comparison of the duration of participation in the trial, adjusted for significant baseline differences showed no significant differences by

TABLE 1 Sociodemographic characteristics by gender at study entry

N (%)	Men ($n = 293$)	Women ($n = 111$)	F or t	df	p-value
Age[a]	22.68 (4.5)	24.33 (6.19)	$t = 2.73$	1	.007
Race			$F = 1.37$	2	.16
White	166 (56.7%)	52 (46.9%)	$F = 1.99$		
Non-white	127 (43.3%)	59 (53.2%)			
Hispanic ethnicity	59 (20.1%)	14 (12.6%)	$F = 1.24$	1	.27
Marital status			$F = 7.42$	1	.007
Presently married	13 (4.4%)	11 (9.9%)			
Widowed/divorced/separated	11 (3.8%)	11 (9.9%)			
Never married	269 (91.8%)	89 (80.2%)		2	
Current residence			$F = 4.48$	1	.011
Independent living	41 (14.0%)	31 (27.9%)			
Supported or structured	12 (4.1%)	2 (1.8%)			
Family, parents, grandparents, sibling	215 (73.4%)	72 (64.9%)			
Homeless, shelter, or other	25 (8.5%)	6 (5.4%)			
Patient's education			$F = 2.37$	2	.094
Some college or higher	83 (28.3%)	42 (37.8%)			
Completed high school	102 (34.8%)	31 (27.9%)			
Some high school	93 (31.7%)	32 (28.8%)			
Some or completed grade school	15 (5.1%)	6 (5.4%)			
Mother's education			$F = 1.75$	2	.17
Some college or higher	130 (44.4%)	37 (33.3%)			
Completed high school	79 (27.0%)	32 (28.8%)			
Some high school or grade school	34 (11.6%)	25 (22.5%)			
No school or unknown	50 (17.1%)	1(15.3%)			
Type of insurance			$F = 3.41$	2	.034
Private	68 (23.4%)	14 (12.7%)			
Public	83 (28.5%)	44 (40.0%)			
Uninsured	140 (48.1%)	52 (47.3%)			

[a]Continuous variable. Unmarked variables are categorical variables.

gender: Men = 13.57 months (SD = 5.46), Women 14.47 months (SD = 8.23), $t = -1.11$, $p = .28$.

Longitudinal analyses examining differences in outcomes by gender (i.e., the interaction of gender by time) showed no significant differences on the primary outcomes of QLS or on total PANSS symptoms (Table 4, column 3) but did show a significantly greater improvement in the intrapsychic functioning sub-scale of the QOL among women ($p < .05$).

Evaluation of differences in treatment effects between women and men (interaction of gender by time and by treatment group) showed no significant differences on any measure of clinical outcome or NAVIGATE service use (Table 4, column 4, Figures 1 and 2).

4 | DISCUSSION

Secondary analysis of RAISE-ETP data on participants with FEP revealed that at study entry women were older with higher QLS scores and better social functioning than men, characteristics that are consistent with previous literature (Seeman, 2019; Thorup et al., 2014; Tseliou et al., 2017).

They also had more severe mood symptoms on the PANSS although not the CDSS (Irving et al., 2021; Tseliou et al., 2017), and reported less use of cannabis but not alcohol or other drugs.

Longitudinal analyses, the primary focus of this study, showed that controlling for these admission differences, there were no significant gender differences in 2-year measures of quality of life, in schizophrenia or depressive symptoms; or in use of key components of NAVIGATE. Furthermore, no gender differences were observed in response to treatment over 2 years.

Previous longitudinal research on gender and schizophrenia suggests that women fare better than men early in the disease course, possibly due to their older age at onset and better adherence and response to antipsychotic medications (Dubreucq et al., 2021; Thorup et al., 2014), though one study showed this advantage fades over time (Thara & Kamath, 2015).

TABLE 2 Community adjustment and quality of life by gender at study entry

N (%)	Men ($n = 293$)	Women ($n = 111$)	F or t	df	p-value
Current student	56 (19.1%)	26 (23.4%)	$F = 0.78$	1	
Currently working	42 (14.3%)	16 (14.4%)	$F = 0.09$	1	.76
Student or working	86 (29.6%)	36 (32.7%)	$F = 0.16$	1	.69
Quality of life[a]			$t = 2.25$	1	
Total score	51.25 (18.54)	56.28 (18.96)			.025
Interpersonal relations	19.26 (8.84)	21.08 (8.18)	$t = 1.94$		.054
Instrumental role	5.14 (6.3)	6.69 (7)	$t = 0.15$		.15
Intrapsychic foundations	20.49 (6.92)	21.7 (7.08)	$t = 0.12$		.12
Common objects and activities	6.36 (2.37)	6.81 (2.12)	$t = 0.0487$		.049
Autonomy support scale mean score[a]	5.53 (1.15)	5.58 (1.38)	$t = 0.3$	1	.77
BEMIB (medication influence and beliefs) mean score[a]	4.95 (1.01)	4.85 (1.05)	$t = 0.75$	1	.45
Mental health recovery measure mean score[a]	4.96 (1.16)	4.74 (1.42)	$t = 1.53$	1	.13
Stigma scale mean score[a]	3.95 (1.15)	4.09 (1.27)	$t = 0.94$	1	.35
Well-being scale mean score[a]	4.01 (0.77)	3.89 (0.86)	$t = 1.25$	1	.21
Current state of MH[a]	63.43 (23.21)	58.78 (24.53)	$t = 0.13$	1	.13
Life as a whole[a]	4.41 (1.41)	4.18 (1.45)	$t = 1.18$	1	.24
Intent to complete the study[a]	7.51 (1.68)	7.33 (2.02)	$t = 1.07$	1	.29
Intent to attend next visit[a]	7.98 (1.54)	7.97 (1.75)	$t = 0.26$	1	.80

[a]Continuous variable. Unmarked variables are categorical variables.

A review of the literature on the association of gender and treatment outcomes in mental disorders other than FEP reveals mixed findings. A general review of Post-Traumatic Stress Disorder (PTSD) treatment outcome studies found equivocal effects of gender (Blain et al., 2010) although a large multi-site study from the Veterans Health Administration reported greater reduction in PTSD symptom scores among female than male Veterans (Stefanovics & Rosenheck, 2020). This finding of superior outcomes for women diagnosed with PTSD has been reported in some additional VA (Eftekhari et al., 2013) and non-VA samples (Bekes et al., 2016; Galovski et al., 2013; Felmingham & Bryant, 2012) and is consistent with the superior social adjustment of women in the baseline data presented here and with other longitudinal studies of FEP (Thorup et al., 2014).

In the realm of substance use disorders, a review of 126 efficacy and effectiveness trials for nicotine dependence found 59 in which women were significantly *less* likely to quit smoking and only two trials that showed women to be significantly more likely to quit smoking than men (Smith et al., 2016).

In the treatment of opioid use disorder women appear to do better than men on measures of both retention in treatment and relapse to drug use. Weinstein and colleagues, for example, reported women were 55% more likely to remain in treatment than men (Weinstein et al., 2017) and a 7-year follow-up study found that women had both greater treatment retention and employment and lower relapse rates than men (Ohlin et al., 2015).

Looking at other psychiatric conditions, Cuijpers and colleagues reported no gender effect on depression outcome after CBT and pharmacotherapy (Cuijpers et al., 2014) and a general review found no gender effect on short- and long-term outcome in anorexia nervosa (Strobel et al., 2018).

This brief review of differences between women and men in studies of mental health disorders other than FEP similarly showed some evidence of superior baseline social adjustment and social adjustment outcomes among women but no consistent pattern of gender differences in treatment effects. This pattern is consistent with the findings of better social adjustment at baseline in this study but no longitudinal differences in service use or outcomes.

4.1 | Limitations

Several methodological limitations require comment. First gender comparisons inevitably require observational research designs since random assignment is not possible. As a result, there may be unmeasured factors that influence outcomes differently among women and men. Since we found no evidence of gender differences in outcomes, after controlling for baseline differences that *were* measured, it seems unlikely that such factors would have altered our main findings. Second the study was not specifically designed to examine gender interactions affecting outcomes and may not have been adequately powered, especially in view of the fact that the sample of women was smaller than that of men. However, the fact that significant interactions have been found in other secondary analyses of the duration of untreated psychosis (Kane et al., 2016) and social class (Bennett &

TABLE 3 Clinical characteristics by gender at study entry

N (%)	Men ($n = 293$)	Women ($n = 111$)	t or F	df	p-value
SCID diagnoses			$F = 3.58$	4	.006
Schizophrenia	162 (55.3%)	52 (46.9%)			
Schizoaffective bipolar	10 (3.4%)	14 (12.6%)			
Schizoaffective depressive	36 (12.3%)	21 (18.9%)			
Schizophreniform provisional or definite	52 (17.8%)	15 (13.5%)			
Brief psychotic disorder	33 (11.3%)	9 (8.1%)			
Lifetime alcohol use disorder			$F = 3.36$	1	.068
Did not meet criteria	178 (60.8%)	79 (71.2%)			
Met abuse or dependence criteria	115 (39.3%)	32 (28.8%)			
Lifetime cannabis use disorder			$F = 9.39$	1	.0023
Did not meet criteria	177 (60.4%)	87 (78.4%)			
Met abuse or dependence criteria	116 (39.6%)	24 (21.6%)			
Number of days of alcohol intoxication[a]	0.4 (2.08)	0.78 (2.87)		1	.15
Number of days of illegal drugs[a]	3.74 (8.07)	1.55 (5.33)		1	.008
Duration of untreated psychosis (weeks)[a]	191.06 (254.96)	199.97 (281.48)	$t = 0.3$	1	.76
Proportion above median duration of untreated psychosis (74 weeks)	142 (48.6%)	60 (54.1%)	$t = -0.97$	1	.33
Any prior hospitalization	39 (16.3%)	14 (17.3%)	$t = 1.03$	1	.30
Prescribed one or more antipsychotics at consent	251 (85.7%)	86 (77.5%)	$F = 3.4$	1	.0661
Days not taking first antipsychotic			$F = 1.67$	2	.19
Few if any, <7	200 (68.7%)	67 (60.4%)			
7 or more	39 (13.4%)	14 (12.6%)			
Not prescribed antipsychotic	52 (17.9%)	30 (27.0%)			
Days taking less than prescribed number of pills			$F = 0.62$	1	.43
Never or almost never, 0%–25%	202 (69.4%)	64 (57.7%)			
Sometimes to always, 26%–100%	37 (12.7%)	17 (15.3%)			
Not prescribed antipsychotic	52 (17.9%)	30 (27.0%)			
Duration of lifetime anti-psychotic medication at consent (days)[a]	43.95 (43.95)	44.54 (50.6)			.89
PANSS symptom severity[a]				1	
Total score	76.82 (14.72)	76.1 (15.82)	$t = 0.76$		.76
Factor scores					
Positive	12.25 (3.91)	12.2 (3.64)	$t = 0.5$		.96
Negative	16.98 (5.14)	15.94 (5.22)	$t = 1.72$		.09
Disorganized/concrete	7.96 (2.68)	7.41 (2.99)	$t = 1.57$		.12
Excited	6.77 (2.83)	6.68 (2.58)	$t = 0.24$		.81
Depressed	7.69 (3.22)	9.01 (3.37)	$t = 3.57$		.0004
CDSS[a]	4.46 (4.35)	5.16 (4.06)	$t = 1.44$	1	.15
CGI[a]	4.04 (0.81)	4.06 (0.85)	$t = 0.28$	1	.78

[a]Continuous variable. Unmarked variables are categorical variables.

Rosenheck, 2020) suggests that the sample was adequate for identifying significant interactions if they existed. Third, although the study was conducted at 34 sites across the US the representativeness of the sample is unknown and thus the generalizability of the results is uncertain. Finally, this study was conducted 5 years after the publication of Kane et al. (2016) using a public release of the data from NIMH and a different analyst (DB) from the original RAISE-ETP analytic team. In contrast to Kane et al. (2016), who use a three-level mixed effects linear regression to model clustered data structure, we use a linear regression with clustered standard errors. This approach allows for an arbitrary correlation between the residuals of observations within a site or over time, which allows us to account for the clustered

TABLE 4 Longitudinal outcomes of women and men in the RAISE-ETP Study and differential response to NAVIGATE treatment (coefficient and standard error [SE])[a]

Outcome or treatment measure: Coefficient (SE)	*N*	Interaction of gender by time[b]	Interaction of gender by time by treatment group[c]
Quality of life scale (total score)	1373	0.0842 (0.1080)	−0.0171 (0.2400)
Interpersonal relations	1376	0.0289 (0.0507)	−0.0175 (0.1180)
Intrapsychic functioning	1374	0.0721 (0.0322)*	−0.0238 (0.0659)
Instrumental role functioning	1375	−0.0237 (0.0472)	0.0396 (0.0846)
Common objects and activities	1374	0.0077 (0.0139)	−0.0070 (0.0243)
PANSS total score	1377	0.0462 (0.0914)	0.1200 (0.2100)
Calgary depression score	1377	0.0216 (0.0201)	−0.0397(0.0343)
Decision support for medications	1329	0.0048 (0.0385)	−0.0035 (0.0058)
Supported employment/education	1324	0.0024 (0.00241)	−0.0003 (0.0052)
Family psychoeducation	1331	−0.0002 (0.00251)	0.0005 (0.0036)
Individual resiliency training participation	1331	0.0012 (0.0034)	0.0075 (0.0049)

[a]Adjusted for age, marital status, living situation, psychotic diagnoses, use of cannabis, use of drugs, number of lifetime psychiatric hospitalizations, depressive symptoms and clustering of observations between sites.
[b]Model includes terms for main effects of gender and time in addition to the interaction term.
[c]Model includes terms for main effects of gender, time and treatment, interactions of time and gender and time and treatment as well as the final three-way interaction term.
*$p < .05$.

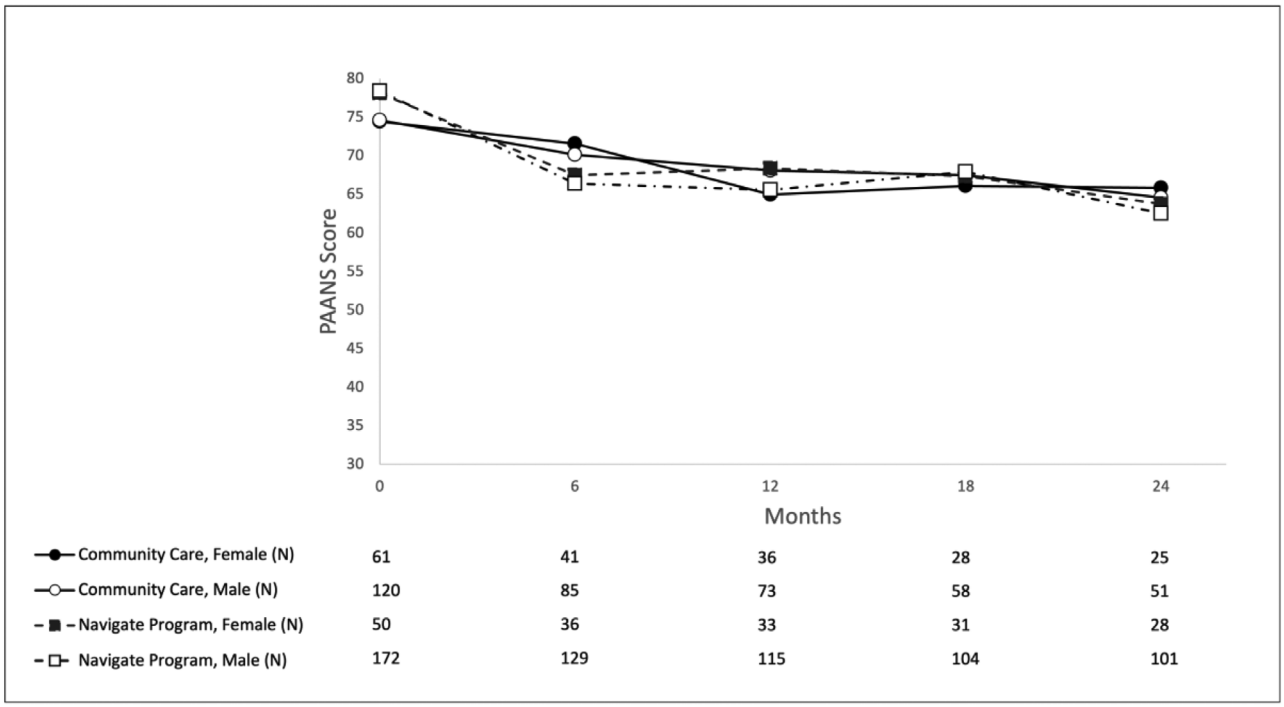

FIGURE 1 PANSS total score by sex and by treatment group including *N* for observations at each point in time

nature of the data while imposing fewer assumptions about the nature of the error structure. The Kane et al. (2016) analysis applies a square root transformation to time, however our analysis does not transform the time trend in this way. Longitudinal analyses were repeated with a square root transformation of time with no change in the results.

5 | CONCLUSION

Secondary analysis of the RAISE-ETP trial found that after adjusting for baseline differences, there were no significant effects of gender on the primary outcome of quality of life, total schizophrenia symptoms, or use of Coordinated Specialty Care services. Perhaps more

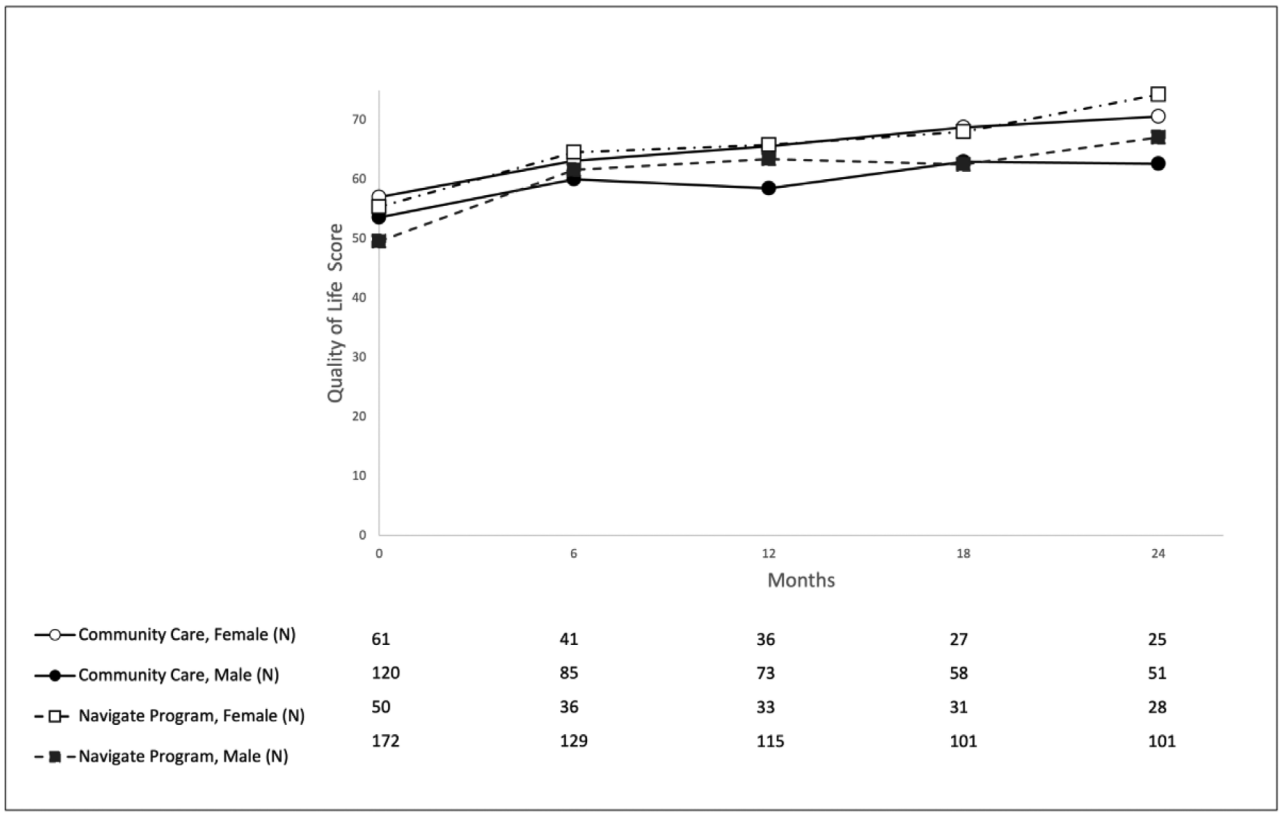

FIGURE 2 QoL total score by sex and by treatment group including *N* for observations at each point in time

importantly, benefits of the NAVIGATE intervention as compared to usual community care also did not differ significantly by gender.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data for this secondary analysis are not publicly available from the authors.

PATIENT CONSENT STATEMENT

The study was approved with a waiver of written informed consent since data are de-identified.

CLINICAL TRIAL REGISTRATION

Clinicaltrials.gov registration NCT01321177.

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