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Parsing the impact of early detection on duration of untreated psychosis (DUP): Applying quantile regression to data from the Scandinavian TIPS study

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ABSTRACT

Background: Prolonged duration of untreated psychosis (DUP) is associated with poor outcomes. The TIPS study halved DUP with an early detection (ED) campaign; however, conventional statistical analyses, focused on mean estimates, failed to reveal the effects of ED across the full DUP distribution, restricting inferences about ED's effectiveness. Utilizing a novel quantile regression based analysis, we examined the differential impact of ED across DUP. Secondary analysis explored possible predictors of DUP, and moderators of the effect of the campaign.
Methods: The TIPS ED campaign was conducted in two health care sectors in Norway, with two equivalent health care sectors serving as controls. Quantile regression analysis was performed to analyze ED campaign's effect.
Results: 281 patients with first episode psychosis were recruited, including 141 from the ED area. ED had no effect on the first quartile (Q1) of DUP, whereas a significant reduction in Q2 (11 weeks), and Q3 (41 weeks) of DUP was observed. The effect of ED was significantly stronger on reducing Q3 than Q1 or Q2, suggesting that the campaign was more effective in longer DUP samples. Male gender and single status predicted longer DUP in Q3: by 38 and 27 weeks, respectively. Single status, but not gender, emerged as a significant moderator of ED campaign effect.
Conclusions: Quantile regression provided in depth information about the non-uniformity, and moderators, of TIPS's ED effort across the full distribution of DUP, demonstrating the value of this analytic approach to re-examine prior, and plan analyses for future, early detection efforts.

1. Introduction

The duration of untreated psychosis (DUP) refers to the period of time between the emergence of psychotic symptoms and initiation of appropriate clinical treatment (Johannessen et al., 2001; Melle et al., 2004). Prolonged DUP is consistently associated with poorer outcomes, including: more severe general, positive and negative symptoms at clinical presentation; reduced likelihood of remission; poorer social functioning; and global outcome (Penttila et al., 2014). This observational evidence has prompted several tests of strategies to reduce DUP

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(Lloyd-Evans et al., 2011; Srihari et al., 2014), and early detection (ED) has emerged as a key priority for mental health services (Dixon et al., 2018).

The Treatment and Intervention in Psychosis (TIPS) study was designed to test an approach to DUP reduction, and to study the effects of this reduction on the course and outcome of psychotic disorders (Hegelstad et al., 2012). The TIPS ED intervention included an intensive information campaign integrated with early detection teams that provided community-based assessment to enable rapid access to care, across two healthcare sectors in Norway. TIPS ED was able to halve DUP compared to two control sites (in Norway and Denmark) that provided equivalent care but without the ED intervention (median, 5 weeks [range, 0–1196 weeks] vs. 16 weeks [range, 0–966 weeks]) (Larsen et al., 2001; Melle et al., 2004). This study also demonstrated a prognostic link between the timing of care and outcomes: at 10 year follow up, a significantly higher percentage of patients from ED sites had recovered i.e. achieved defined standards of symptom remission and social and role functioning (Hegelstad et al., 2012; Joa et al., 2007; Larsen et al., 2011; Melle et al., 2006; Ten Velden Hegelstad et al., 2013).

These results imply that early detection can confer a significant and lasting advantage for patients with psychotic disorders. However, the differential effectiveness of ED campaigns in reducing delay across the spectrum of DUP has not yet been examined. This leaves open the question of 'what works for whom' in terms of shortening a prognostically important variable. Also, separate from its potential impact on treatment outcome, the time between onset of frank psychosis and entry into stable clinical care can be a period of 'destructive chaos' (McGlashan, 1999) with significant distress in the young person and family, elevated risk for impulsive self-harm and aggression, and potentially catastrophic social losses, including incarceration, and the loss of employment, college placement or relationships. Understanding better which subgroups benefit from ED is necessary to refine such efforts, and further minimize suffering and disability.

Previously, we demonstrated that quantile regression (QR) can both manage skewed distributions and allow analysis for meaningful heterogeneity in DUP (Guloksuz et al., 2016). Unlike ordinary least-squares regression, which focuses on the conditional mean response, QR can estimate the heterogeneous effects of predictors (e.g., age, sex, education, or ED) across different quantiles of outcome (DUP), rather than presuming a uniform mean effect. Furthermore, unlike linear regression that relies on a normality assumption, QR can provide more accurate estimates in samples with extreme outliers, as is common in DUP distributions.

The current study aims to leverage quantile regression to analyze the impact of a seminal ED campaign, across the DUP distribution. Data is drawn from the first experimental approach to demonstrate DUP reduction: the Scandinavian Treatment and Intervention in Psychosis (TIPS) study (Melle et al., 2004). We hypothesized that the effectiveness of TIPS' ED campaign would vary across different quantiles of DUP. The secondary aim of this analysis is to explore if this differential impact across DUP quantiles is moderated by demographic, clinical, premorbid and social factors.

2. Method

2.1. Design of the treatment and intervention in psychosis (TIPS) study

The TIPS study was a prospective clinical trial which included three first-episode psychosis centers across four Scandinavian healthcare sectors: Rogaland County, Norway, Ulleval sector, Oslo, Norway and Roskilde county, Denmark (Joa et al., 2008). The Rogaland sector was the experimental site, having developed an early detection (ED) system to reduce DUP in a catchment area of 370,000 inhabitants. The TIPS project established a comprehensive, multi-level, information, education and service delivery system which began on January 1st, 1997 and ended on December 31, 2000. Ulleval and Roskilde were the control sectors, with a combined total of 295,000 inhabitants. Here, ED campaign was not implemented, and they relied on usual detection and referral systems for first episode cases. The populations of the health care sectors showed comparable characteristics regarding age and sex distribution, main income levels and unemployment rates. Participants from the ED area were less likely to be immigrants from a non-western country (4% vs 12%), to be educated beyond high school (21% vs 31%), and live in urban areas (84 vs 96%) (Melle et al., 2004). The incidence of schizophrenia for Rogaland county was estimated to be 5.5/100,000 in 1982–1983 (Johannessen, 1985). As expected, since the campaign promoted a lower threshold for help seeking, the number of persons undergoing screening was higher in the ED area, but those who were eligible for the study were fewer (186 [50/100,000] vs 194 [66/100,000] in the No-ED area). Incidence varied across the years and within the two areas: this may have been due to natural variation in the base rate of relatively rare disorders, or the higher degree of urbanization in the No-ED area compared to the ED area (Melle et al., 2004).

The ED intervention consisted of messaging about recognition and treatment for psychotic symptoms that targeted the general population via newspaper advertisements, and schools and general practitioners via outreach. Specialized low threshold early detection teams could be activated by a single phone call from potential patients, families, or friends. These teams responded with rapid assessments in community settings, and facilitated transfer to specialized treatment teams. Inclusion criteria and assessments are detailed elsewhere (Melle et al., 2008).

2.2. Definition of duration of untreated psychosis

DUP was determined at study entry from all available information, including semi-structured interviews with patients and relatives, and medical records. DUP was defined as the time, in weeks, from psychosis onset to the start of adequate treatment. Onset of psychosis was equated with the first appearance of positive psychotic symptoms, defined as the first week with symptoms corresponding to a Positive and Negative Syndrome Scale (PANSS) score of 4 or more on at least one of the positive subscale items 1 (delusions), 3 (hallucinatory behavior), 5 (grandiosity), or 6 (suspiciousness/persecution) or general subscale item 9 (unusual thought content). Adequate treatment was defined as a structured course of antipsychotic medications or hospitalization in highly staffed psychiatric wards organized to manage disturbing psychotic symptoms (Melle et al., 2004). A few non-hospitalized patients enrolled in outpatient psychotherapy that was structured and directed toward psychosis, but declined antipsychotic medication. For these patients, the initiation of such psychotherapy was coded as the start of adequate treatment (Simonsen et al., 2010). For the rare cases with prior brief and self-remitting psychotic episodes, the lengths of these episodes were included in the DUP estimate.

2.3. Statistical analysis

Demographic, social and clinical characteristics of enrolled patients were compared across ED and no-ED areas. Quantile Regression (QR) was used to model the relationship between various independent variables and conditional quantiles of response. The impact of ED was examined across the full range of DUP, and particular effects on Q1, Q2 and Q3 are presented. We further examined the statistical significance of the heterogeneity of ED's effect on DUP using the Wald test (Koenker and Bassett, 1978), which provides a χ^2 statistic with degrees of freedom, and p values for tests of differences. We conducted secondary analyses to evaluate baseline predictors of DUP quartiles, as well as moderators of ED effects across quartiles using interaction terms in the QR model. Sociodemographic terms included: age, gender, marital status (single vs. other, including: separated/divorced/living with partner/married), family contacts (from 1 = never, to 5 = daily) (Simonsen et al., 2007), and objective financial adequacy as measured by the Lehman Quality of Life Interview (L-QoLI) (Melle et al., 2005).

Table 1
Differences of baseline characteristics between participants coming from the Early Detection (ED) and the No-ED area.

	No-ED	ED	p value
	(n=140)	(n=141)	
Age at study entrance, Mean(SD)	31.1(10.5)	26.2(7.6)	<.0001
Gender, male	79(56.4%)	87(61.7%)	0.37
Marital status, single[a]	88(62.9%)	109(77.3%)	0.008
DUP weeks, median [IQ]	16 [3,66]	5 [2,26]	
mean (SD)	56.5(118.3)	41.6(122.8)	0.30
Diagnostic distribution			0.15
Schizophrenia	41(29.3%)	39(27.7%)	
Schizophreniform disorder	30(21.4%)	31(22.0%)	
Schizoaffective disorder	12(8.6%)	22(15.6%)	
Affective psychosis	21(15.0%)	19(13.5%)	
Delusional disorder	9(6.4%)	6(4.3%)	
Brief Psychotic Episode	6(4.3%)	13(9.2%)	
Psychosis NOS	21(15.0%)	11(7.8%)	
Narrow schizophrenia spectrum diagnosis	83(59.3%)	92(65.2%)	0.30
GAF_function, mean (SD)	28.76(9.72)	33.63(10.01)	<.0001
GAF_symptom, mean (SD)	27.13(6.88)	30.96(6.36)	<.0001
PANSS score, mean (SD)			
PANSS_total_score	76.80(19.68)	64.28(13.46)	<.0001
PANSS_negative scale	16.64(7.47)	13.86(5.70)	0.0005
PANSS_positive scale	21.66(5.64)	18.81(4.93)	<.0001
PANSS_general scale	38.42(10.38)	31.57(7.64)	<.0001
PAS score, mean (SD)			
PAS social level change	0.78 (1.30)	0.89(1.57)	0.54
PAS academic level change	0.52(1.29)	0.65(1.22)	0.40
PAS_social_cluster			0.82
missing	4(.%)	4(.%)	.
Good Stable	61(44.9%)	64(46.7%)	.
Intermediate Stable	26(19.1%)	23(16.8%)	.

Clinical variables included: presence of core schizophrenia-spectrum diagnoses and premorbid functioning, measured with the Premorbid Adjustment Scale (PAS). PAS scores were divided into two domains: Academic and Social, each categorized as good, intermediate or poor (initial level) and whether the course was stable or deteriorating (change) (Larsen et al., 2004). Also, global psychopathology was assessed with the PANSS total score and subscales (positive symptoms, negative symptoms, general symptoms), and overall functioning was evaluated with the Global Assessment of Functioning (GAF) scale, that provided GAF symptom and GAF function scores (Joa et al., 2008; Pedersen and Karterud, 2012).

SAS 9.4 (Cary, NC) was used for all statistical analyses(SAS Institute., 2017). The statistical significance level was set at $p < 0.05$, two-sided.

3. Results

3.1. Baseline characteristic of the sample

Altogether, 281 patients were included, 141 belonging to the early detection (ED) area. Compared to residents of no-ED areas, ED exposed samples were younger (mean age 26 vs. 31; $P < 0.0001$). The two groups showed no difference with respect to affective vs. non-affective psychosis diagnoses; however, participants coming from the ED area presented with significantly lower psychopathological symptom severity and better global functioning (Melle et al., 2004), as detailed in Table 1 and previously reported (Melle et al., 2004).

3.2. Differential impact of ED campaign on DUP

Fig. 1A and B display the differential impact of ED campaign between ED and No-ED samples across the entire distribution of DUP. In the No-ED sample, Q1 = 3 weeks, Q2(median) = 16 weeks and Q3 = 66 weeks. Within the ED sample, Q1 = 1.5 weeks, Q2(median) = 5 weeks and Q3 = 26 weeks. The widths of the 95% confidence interval bands differ across quantiles, illustrating the advantage of QR in revealing the heterogeneous effects on different quantiles in contrast to traditional analyses that assume homogenous effect across the entire distribution of the outcome. In addition, Fig. 1B shows that the upper band of 95% CI at Q2 and Q3 are away from 0 effect, respectively −4.6 weeks for Q2, and − 10.4 weeks for Q3.

As outlined in Table 2, QR analysis revealed that ED had no discernible effect on DUP in the first quartile (Q1), but engendered a significant reduction in the second quartile (Q2 or median: 11 weeks reduction, 95% CI -17.4 to −4.6, $P = 0.0008$), and the third quartile (Q3: 41 weeks reduction, 95% CI -71.6 to −10.4, $P = 0.009$). Moreover, the effect of ED was significantly stronger in Q3 vs. Q1 ($P = 0.009$), Q3 vs Q2 ($P = 0.03$) and Q2 vs. Q1 ($P = 0.006$), suggesting that the effect of ED was stronger for longer DUPs.

3.3. Predictors of DUP

We evaluated potential associations between baseline characteristics and DUP quartiles. Male gender was associated with longer DUP (Table S1), and in the higher quartiles: males endured a DUP that was 7 weeks longer in Q2 (95% CI -13.2 to −0.79, P = 0.03) and 38 weeks longer in Q3 (95% CI −68 to −8, $P = 0.01$) (Table 3). Also, single participants had a DUP 27 weeks longer in Q3 (96% CI -53.7 to 0.3, $P = 0.04$).

We also explored associations between clinical variables and DUP quartiles (supplemental material, Table S2): higher initial PAS academic

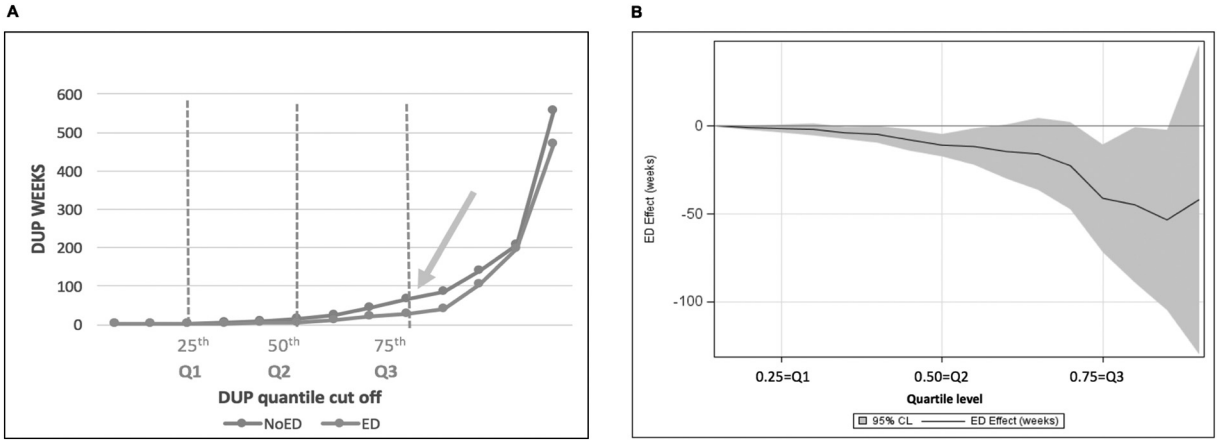

Fig. 1. Differential impact of Early Detection (ED) across quartiles of the Duration of Untreated Psychosis (DUP). **A**. Early Detection (ED) campaign was significantly associated with a reduction in DUP in the second (Q2) and third quartile (Q3) of DUP. The arrow highlights the stronger effect of ED campaign on subjects with longer DUP. **B.** The blue band shows the 95% confidence intervals of the group difference corresponding to each quartile. Q1 = 25th percentile, Q2 = 50th percentile, Q3 = 75th percentile (X axis).

Table 2
Differential effect of early detection (ED) campaign on quartiles of the Duration of Untreated Psychosis (DUP) (in weeks) in the whole sample.

	Duration of Untreated Psychosis (weeks)			
Quartile	ED-No-ED: Difference (95% Cl)	P value	P value (compared to Q1)	P value (compared to 02- median)
Q1 (25%)	-1.5 (-3.7, 0.7)	0.18	-	-
Q2-Median (50%)	-11.0 (-17.4, -4.6)	0.0008	0.0006	-
Q3 (75%)	-41.0 (-71.6, -10.4)	0.009	0.009	0.03

Q1, 2, 3=Quartiles of Duration of Untreated Psychosis (DUP).

Table 3
Results of predictors of Duration of Untreated Psychosis (DUP) quartiles in the whole sample. Male and single status are associated with both lower median and Q3 of duration of untreated psychosis (DUP). Comparisons of the different effect of the predictor within quartiles are also reported.

	DUP Quartile	DUP Difference weeks (95% Cl)	P value	P value (compared to Q1)	P value (compared to Q2)
Gender, (Male < Female)					
	Q1 (25%)	-2 (-3.5, -0.5)	0.009	-	-
	Median (50%)	-7 (-13.2, -0.79)	0.03	0.07	“
	Q3 (75%)	-38.0 (-68.0, -8.0)	0.01	0.02	0.02
Marital status[a], (Single < Nonsingle)					
	Q1 (25%)	-1 (-2.3, 0.3)	0.12	-	-
	Median (50%)	-4.9 (-11.2, 1.4)	0.13	0.18	-
	Q3 (75%)	-27.0 (-53.7, -0.3)	0.048	0.05	0.06

[a] Non-single group includes married, separated, divorced, widowed.

level scores (or worse premorbid academic functioning) or having a narrow schizophrenia spectrum diagnosis was associated with longer DUP across all quartiles; higher scores in PANNS total and general symptoms subscales at clinical presentation (or higher symptom severity) was associated with a slightly longer DUP across the upper quartiles. Higher baseline GAF symptom and function scores were associated with longer DUP in the lower and median quartiles.

3.4. Moderators of ED effect on DUP

Moderation effects of gender on ED efficacy were evaluated after controlling for age and marital status. After splitting the sample by gender, a statistically significant reduction of DUP was observed only for male participants in Q3 (−48.1, 96% CI −90.5 to −5.6, P = 0.03) in the ED vs. no-ED areas (Table 4). The distribution of DUP is detailed in Table S3. A large difference of 43.3 weeks in the reduction of DUP in Q3 between males and females did not reach the conventional threshold for statistical significance.

Moderation effects of marital status on ED efficacy were evaluated after controlling for age and gender. After splitting the sample by marital status, a statistically significant reduction of DUP was observed only for singles in Q3 (difference at Q3 = −48.2 weeks; 95% CI −79.7 to −16.7, $P = 0.003$) (Table 4). The distribution of DUP is detailed in Table S3. The difference of the effect of ED among singles in Q3 differed statistically from the effect among non-single (difference in DUP effect = −50.3 weeks; 95% CI −93.3 to −7.3, $P = 0.02$). Thus, singlehood was a significant moderator of ED's impact on the longest extreme of the DUP distribution.

Additional exploratory analyses were performed to detect other clinical and social moderators of the effect of the ED campaign across quartiles of DUP, after controlling for age, gender and single status (Table 5). Higher objective financial adequacy was associated with longer DUP in the lowest quartile of the ED cohort (2 weeks increase, $P = 0.04$), but had no impact in other quartiles. The effect of ED in Q1 of DUP was greater with increasing episodes of arrest by police. Each adjunctive episode of arrest was associated with more DUP reduction only in Q1 (12.3 weeks, $P = 0.047$). A more severe clinical presentation, being diagnosed with a narrow schizophrenia spectrum diagnosis, and premorbid functioning (both social and academic) were not moderators of ED across the DUP quartiles. Number of family contacts also did not moderate ED effects across DUP quartiles.

4. Discussion

This is the first study to interrogate the differential impact of an early detection intervention across a full DUP distribution. As hypothesized, we were able to show that TIPS' successful ED campaign did not have a uniform effect. DUP reduction appeared to follow a graded response: not observed in those with short DUP, with significant effects of increasing magnitude in the second (11 weeks reduction) and third quartiles

Table 4
Do gender[a] and marital status[b] moderate the impact of Early Detection (ED) on Duration of Untreated Psychosis (DUP) across the quartiles?

DUP Quartile	ED campaign effect among males	ED campaign effect among females	Difference
Q1 (25%)	-4 (-8.5, 0.5) P=0.08	0 (-1.9, 1.9) P=1.00	-4.0 (-8., 0.9) P=0.11
Median (50%)	-17.1 (-35.4, 1.2) P=0.07	-5.1 (-13.5, 3.26) P=0.23	-12.0 (-32.0, 8.0) P=0.24
Q3 (75%)	-48.1 (-90.5, -5.6) P=0.03	-4.8 (-30.4, 20.9) P=0.71	-43.3 (-92.8, 6.23) P=0.09
DUP Quartile	ED campaign effect among single	ED campaign effect among non-single[c]	Difference
Q1 (25%)	-3.6 (-8.2, 1.0) P=0.12	-1.0 (-3.2, 1.2) P=0.37	-2.6 (-7.6, 2.5) P=0.32
Median (50%)	-14.3 (-30.5, 1.8) P=0.08	-1.0 (-8.7, 6.7) P=0.80	-13.3 (-31.1,4.5) P=0.14
Q3 (75%)	-48.2 (-79.7, -16.7) P=0.003	2.1 (-27.2, 31.3) P=0.89	-50.3 (-93.3, -7.3) P=0.02

[a] adjusted for age and marital status.
[b] adjusted for age and gender.
[c] Non-single group includes married, separated, divorced, widowed. DUP is measured in weeks.

Table 5
Exploring other possible clinical and environmental moderators of the ED campaign effect (reduction of DUP), across DUP quartiles, after controlling for age, gender and single status. The effect modification is presented here with its 95% confidence interval as extent of increase (positive values) or decrease (negative values) in DUP (measured in weeks) in the ED cohort, per every unit increase in moderator.

Moderators	Effect modification at Q1 (95% CI)	*P* value	Effect modification at Q2 (95% CI)	P value	Effect modification at Q3 (95% CI)	P value
Narrow schizophrenia spectrum diagnosis (Yes vs. No)	−1.0 (−6.3, 4.3)	0.71	−11.3 (−27.5, 5.0)	0.17	−23.4 (−75.2, 28.3)	0.37
PAS social level childhood	−0.2 (−2.4, 1.9)	0.84	3.7 (−4.9, 12.2)	0.40	−3.0 (−39.4, 33.3)	0.87
PAS social level change	−1.0 (−2.5, 0.5)	0.19	−2.7 (−8.6, 3.3)	0.38	−8.7 (29.0, 11.7)	0.40
PAS academic level childhood	−1.9 (−4.3, 0.5)	0.12	−3.8 (−12.8, 5.1)	0.40	−7.0 (−42.1, 28.0)	0.69
PAS academic level change	−0.8 (−2.5, 0.9)	0.33	−0.5 (−5.7, 4.7)	0.84	4.5 (−10.2, 19.1)	0.55
GAF_symptom	−0.2 (−0.5, 0.1)	0.18	−0.5 (−1.6, 0.6)	0.38	−0.7 (−3.7, 2.3)	0.67
GAF_function	−0.2 (−0.4, 0.1)	0.18	−0.3 (−0.9, 0.4)	0.46	−0.3 (−2.6, 2.1)	0.83
Number of family contacts	1.0 (−0.8, 2.8)	0.27	3.1 (−2.0, 8.2)	0.23	6.3 (−14.9, 27.5)	0.56
Objective financial adequacy	2.0 (0.1, 3.8)	0.04	2.2 (−2.6, 7.0)	0.36	5.3 (−15.5, 26.1)	0.62
Episodes of arrest by police	−12.3 (−24.4, 0.1)	0.047	−6.7 (−15.7, 2.3)	0.14	−53 (−187.1, 81.1)	0.44

Note. DUP = Duration of Untreated Psychosis. Q 1,2,3 = DUP quartiles 1, 2, 3. PANNS = The Positive and Negative Syndrome Scale. CI=Confidence Interval.

(41 weeks reduction). TIPS' previously reported success in reducing DUP thus appears largely due to effects in the longer tail of the DUP distribution. Hence, a vulnerable subgroup i.e., those suffering the greatest delays in accessing care for the distressing and potentially life-disrupting symptoms of psychosis, benefited the most from this ED effort. This is a reassuring inference about the potential public health impact of such campaigns. Also, the use of Quantile Regression (QR), to parse the impact of early detection, offers additional useful insights (outlined below) and should be considered in the design of future campaigns.

The distribution of DUP in the whole sample showed significant sociodemographic differences: TIPS recruited men, and singles (across genders) with significantly longer DUP in the upper tail of the distribution (Q3). When dividing the sample by gender, DUP was found to be significantly reduced by ED only in men in Q3 (by 48.1 weeks). However, gender was not found to be a significant moderator of EDs greater impact on longer DUPs. These results add to the mixed findings about the role of gender in affecting the length of DUP (Cascio et al., 2012). However, the lack of statistically significant DUP reduction in women merits further consideration: it is possible that the messaging and media channels used by the TIPS campaign were more accessible to men than women, or that the campaign reached the targeted female audience, but stigma or other barriers to accessing treatment were differentially greater for women. Qualitative studies have suggested obstacles unique to women seeking FEP treatment: e.g. the threat of loss of child custody, and gender stereotypes (e.g. being labelled as "overdramatic") (Chernomas et al., 2017; Diaz-Caneja and Johnson, 2004; Hagen and Nixon, 2011). While these and other gender specific factors are expected to vary across cultures and regions, such interrogations of prior DUP data across the distribution can inform ED campaigns and FEP services e.g., to reinforce the value of their parenting role, target psychosis onset that could emerge in the context of childbirth, and to offer multidisciplinary services that can meet many needs at one site (Chernomas et al., 2017).

A more reassuring interpretation of the gender disparity disfavoring women in ED effectiveness is a possible floor effect. Men in the ED area showed similar (median) or even longer (Q1 and Q3) DUP compared to women in the No-ED area, suggesting the need to focus on barriers specific to men. While the data on greater reduction of DUP in men suggests that these barriers are modifiable to a significant degree, there is clearly more ground to cover to catch up with female enrollees in first episode care. Overall, these data support tailoring of ED campaigns toward assessing and responding to the specific needs of each gender.

Marital status played an important role in the effect of ED. Single patients tended to have longer DUPs and also benefited the most in terms of size of DUP reduction in the longest quartile. Singlehood also positively moderated DUP reduction in this quartile, adding a new and unexpected finding to a recent meta-analysis on factors influencing the effect of DUP reduction interventions (Oliver et al., 2018). More frequent family contacts were observed in participants coming from the ED area, however number of family contacts did not seem to moderate the effect of TIPS ED on DUP quartiles. Factors such as living with someone, and proactive social networks (Peralta et al., 2005) have been reported, in other samples, to play a significant role in accelerating access to care for a target population that is young and often unmarried. While this makes the longer DUPs in the single sample here unsurprising, the selectively greater impact of TIPS ED on this subgroup is a welcome finding. The moderator analyses did not show significant effects for narrow schizophrenia diagnosis, and other clinical and premorbid variables across the DUP quartiles. However, the exploratory nature of this post-hoc analysis of DUP suggests caution in overinterpreting positive or negative effects.

This analysis demonstrates the utility of quantile regression to reveal meaningful differential effects of an ED campaign across an entire DUP distribution. First, the magnitude of differences in delays to care in the upper vs. lower quartiles of DUP would be recognized by most clinicians and caregivers as important. Second, subsets of participants, because of gender or marital status, appeared to have been less responsive to this campaign, offering a basis to refine ongoing or future campaigns. Third, the majority of ED efforts have reported a lack of overall change in DUP (Lloyd-Evans et al., 2011). The analysis modeled here might recover more granular information on positive impacts on portions of the DUP distribution across subgroups that may support continuation and refinement of valuable efforts that would otherwise be deemed unsuccessful.

Additionally, such subgrouping can be helpful for future ED campaigns that are able to use social media channels to target messaging in ways that were unavailable during the TIPS study. There is increasing use of the internet and social media (Kemp, 2019), in particular among teens (Anderson and Jiang, 2018), and there is growing evidence that young people affected by psychosis use social media to obtain health information (Birnbaum et al., 2016). The ability afforded by these digital media channels to iteratively adapt messaging, and target specific population segments can leverage QR-based identification of subgroups that are differentially responsive to ongoing ED efforts and enable more dynamic, ecologically responsive campaign designs (Srihari et al., 2014).

Our analysis did not find a significant effect of ED campaign in quartile 1 of DUP. Aside from a floor effect, another possibility might have to do with mode of onset: the shortest quartile may have included a greater proportion of individuals with rapidly escalating positive symptoms, that more quickly drew clinical attention regardless of the presence of an ED campaign.

Several cautions must be made in the interpretation of these results. As a post-hoc analysis, the findings are not definitive evidence but present plausible inferences from prior studies or more defensibly, hypotheses that can be built into the design of future studies of early detection (Srihari et al., 2014). Also, the lack of ability to detect a significant effect

of ED in the shorter end of the DUP distribution (Q1 = 2 weeks) may have been related to the use of weeks rather than days (Large et al., 2008) as a unit of measurement in the TIPS study.

4.1. Conclusion

QR revealed that, across the length of DUP, the effect of TIPS' ED intervention varied significantly. It also showed the potential to provide new information about clinical and social moderators across the length of DUP that could become crucial in targeting intervention for reducing the burden of disease in first episode of psychosis. Previous ED campaigns (Malla et al., 2005; McGorry et al., 1996) have not been as successful as TIPS in showing a significant effect across a median DUP on a population level. It is possible however, that a similar analysis across quartiles might reveal impact in some parts of the overall distribution. Conversely, campaigns that show overall success might use this approach to discover underserved subgroups. Further, the use of QR can help assess for moderators of these differential effects, and inform tailoring of future ED efforts.

Contributors

MF, FL, SG, CT, VS designed the analysis. MF and SB managed the literature searches. FL undertook the statistical analyses. MF wrote the first draft of the manuscript. TIPS investigators (SF, WVH, IJ, JOJ, IM, ES) contributed to the interpretation of the results. All authors contributed to, and approve, the final manuscript.

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Declaration of Competing Interest

Svein Friis has received an honorarium as a data consultant with the RAND Corporation for a project sponsored by Janssen-Cilag pharmaceutical company. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.035.

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