Mixed-effects models reveal prediction of long-term outcome by duration of untreated psychosis (DUP) and illness (DUI) varies with quantile gradation but is invariant with time across 7 years in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

Nnamdi Nkire a,b, Tara Kingston a,b, Anthony Kinsella b, Vincent Russell c, John L. Waddington b,d,*

a Cavan-Monaghan Mental Health Service, Drumalee Primary Care Centre, Cavan, Ireland
b School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, Ireland
c Department of Psychiatry, RCSI University of Medicine and Health Sciences, Beaumont Hospital, Dublin, Ireland
d Jiangsu Key Laboratory of Translational Research & Therapy for Neuro-Psychiatric-Disorders and Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou, China

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ABSTRACT

While associations between duration of untreated psychosis (DUP) and outcome have been widely reported, how long these relationships endure following initiation of treatment and how such associations are distributed across the range of DUP values encountered remain unclear. This study investigates prospectively (i) whether prediction of outcome by DUP and by duration of untreated illness (DUI) diminishes, remains stable or increases in the long term after initiating treatment, and (ii) whether these relationships for differing indices of outcome vary across gradations of DUP-DUI values. Sixty-two subjects were evaluated prospectively for DUP, DUI, premorbid features, psychopathology and quality of life at both first episode psychosis (FEP) and at 7-year follow-up; functionality and service engagement were assessed at follow-up. Data were analysed using mixed-effects models for DUP and DUI quantiles. Prediction by longer DUP and DUI of greater psychopathology, particularly negative symptoms, and lower quality of life remained stable between FEP and follow-up; longer DUP and DUI also predicted lower functionality and service engagement at follow-up. While most associations were confined to the longest DUP-DUI quartile, those between DUP-DUI and negative symptoms and quality of life were distributed in a graded manner across DUP-DUI quartiles. Material confounding with premorbid features, including lead-time bias, was not supported. These findings suggest that benefits of reducing DUP-DUI may endure for at least a decade beyond FEP and that even modest reductions in DUP-DUI may confer particular advantage in the more debilitating and intransigent domain of impairment.

1. Introduction

Early intervention services (EIS) for first episode psychosis (FEP) are in part predicated on evidence that longer duration of untreated psychosis (DUP) is associated with greater impairment in terms of psychopathology and related indices (Hegelstad et al., 2012; Penttila et al., 2014; Clarke et al., 2016; Correll et al., 2018; Howes et al., 2021; Srinhari et al., 2022). EIS may also confer additional benefit in terms of judicial outcome (Pollard et al., 2020) and we have reported health economic advantage using the net benefit approach (Behan et al., 2020). DUP has been most widely investigated in relation to clinical assessments made at FEP and during the early course of subsequent illness, with the relationship between longer DUP and greater impairment appearing most robust during the initial phase of untreated psychosis (Drake et al., 2020). However, of critical importance, yet still unclear, is the extent to which initial associations between DUP and degree of impairment endure across the long-term course of psychotic illness, with the most recent meta-analyses indicating that such associations with DUP may be evident at a median of three years post-FEP (Penttila et al., 2014; Howes et al., 2021). While some studies have addressed relationships between

* Corresponding author at: School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland.
E-mail address: jwadding@rcsi.ie (J.L. Waddington).

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DUP and outcome after longer intervals of up to 10–12 years (Hill et al., 2012; Jabar et al., 2021), there remain uncertainties as to whether these relationships decrease, remain stable or increase between FEP and long-term follow-up; most studies have analysed relationships at individual time points, rather than including time as a repeated measure. Also, it remains unclear whether relationships between DUP and outcome generalise across or are restricted to particular domains of outcome, to include functionality and quality of life, with the domain of service engagement remaining substantially unexplored.

Additionally, it is not clear whether associations between DUP and outcome are distributed uniformly across the range of DUP encountered or vary with particular gradations of DUP within that range (Penttila et al., 2014; Howes et al., 2021). Furthermore, long-standing concerns as to whether DUP may be not a direct predictor of outcome but, rather, confounded with aspects of the early course of illness such as premorbid features (Penttila et al., 2014; Howes et al., 2021) have been recently augmented by related concerns regarding lead-time bias (Jonas et al., 2020). Finally, the potentially more insidious variable of duration of untreated illness (DUI), which adds to DUP the length of the psychosis prodrome, has received little attention (Clarke et al., 2016; Nkire et al., 2021a).

Therefore, it is important to further clarify relationships between DUI and outcome beyond FEP, in a manner analogous to those for DUP.

The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS; Baldwin et al., 2005; Nkire et al., 2021b) is embedded within the real-world setting of the Irish public mental health services and sought to identify and assess an epidemiologically representative population of incident FEP. We have recently described, for the first time, a systematic epidemiological and clinical comparison between all 12 DSM-IV psychotic diagnoses in terms of psychopathology, neuropsychology, neurology, premorbid intellectual function, premorbid adjustment, quality of life and insight (Nkire et al., 2021b). Subsequently, we have conducted a systematic comparison of DUP vs DUI in terms of their associations with these clinical assessments at FEP (Nkire et al., 2021a).

Subjects incepted over the early years of operation of CAMFEPS were then re-assessed at long-term follow-up (Kingston et al., 2013, 2018). In an independent cohort, we have recently reported that associations between DUP and outcome may endure across two decades (O’Keeffe et al., 2022). We here elaborate these findings in the CAMFEPS cohort by (i) systematically applying mixed-effects models for clinical assessments of psychopathology and quality of life made prospectively from FEP to 7-year follow-up in relation to both DUP and DUI, (ii) analyzing by quantiles whether variations in outcome are distributed uniformly across the range of DUP and DUI or vary with particular gradations of DUP or DUI within that range, (iii) extending assessments at outcome to functionality and service engagement, and (iv) clarifying the extent of confounding with premorbid features and/or lead-time bias in these associations.

2. Method

2.1. Participants and study design

The Research Ethics Committees of the North Eastern Health Board [and, following restructuring, of the Health Service Executive Dublin North East Area], St. Patrick’s Hospital, Dublin, St. John of God Hospital, Co. Dublin, and the Central Mental Hospital, Dublin, gave their approval for these studies. All subjects gave written informed consent to assessment after the study had been fully explained. They were incepted from the age of 16 throughout the adult lifespan, with no arbitrary upper age cut-off. Informed consent was also sought from a parent or guardian for those aged 16 or 17.

This report involves the long-term follow-up of cases incepted into CAMFEPS, a prospective study that sought to identify ‘all’ incident cases presenting with FEP in two rural counties in Ireland, Cavan and Monaghan, as described previously in detail (Baldwin et al., 2005; Nkire et al., 2021b). These two contiguous counties share an unusually uniform socioeconomic milieu, i.e. a predominantly white Irish population, minimal immigration and the absence of urban centres. Identification of cases involved all routes to care, i.e. via public, private or forensic services, and whether receiving home-based, outpatient or inpatient treatment. Ascertainment and evaluation of subjects, systematic comparisons across all 12 DSM-IV psychotic diagnoses, and systematic comparison of associations between DUP, DUI and clinical assessments at FEP have been described previously for the CAMFEPS cohort (Nkire et al., 2021a, 2021b). Evaluation of long-term outcome for subjects incepted into CAMFEPS during its early years of operation has also been described previously (Kingston et al., 2013, 2018). This is the first report on longitudinal relationships between assessments from FEP through to long-term outcome in relation to DUP and DUI.

2.2. Assessment instruments

At FEP, following diagnostic evaluation using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995), the scale of Beiser et al. (1992) was used to assess DUP and DUI. DUP was defined as the period between emergence of first noticeable psychotic symptoms and receipt of antipsychotic treatment; DUI was defined as the period between first noticeable symptoms and receipt of antipsychotic treatment, i.e. DUI = length of prodrome + DUP. As previously described (Nkire et al., 2021a), completion of this scale included information from multiple sources: face-to-face interview with the patient regarding illness and psychosis onset; review of all medical records; interview with initial clinicians where possible; and interview with family and friends where available and able to give information regarding illness and psychosis onset. Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) and premorbid intelligence was assessed using the National Adult Reading Test (NART; Nelson, 1982).

Assessments made both at FEP and at long-term follow-up in relation to DUP vs DUI are as described previously in detail (Nkire et al., 2021a, 2021b; Kingston et al., 2018). In outline, psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) to give subscale scores for PANSS-Positive (P), PANSS-Negative (N) and PANSS-General (G) symptoms (Kay et al., 1987). Quality of life was assessed using the Quality of Life Scale (QLS; Heinrichs et al., 1984).

Assessments made only at long-term follow-up in relation to DUP vs DUI are as described previously in detail (Kingston et al., 2018). In outline, functionality was assessed using four instruments: the Global Assessment of Functioning Scale (Spitzer et al., 1996); the Health of the Nation Outcome Scale (Wing et al., 1996); the Strauss-Carpenter Scale (Strauss and Carpenter, 1972); and the Specific Level of Functioning Scale (Schneider and Struening, 1983). Service engagement was assessed using the Service Engagement Scale (SES; Tait et al., 2002).

2.3. Statistical analysis

Data are expressed as means and standard deviations (SD), with the addition of medians, interquartile ranges (IQR) and ranges for DUP and DUI. As described previously (Nkire et al., 2021a), analyses were carried out on compositing the five most populous psychotic diagnoses, i.e. schizophrenia (SZ), schizoaffective disorder (SF), schizoaffective disorder (SA), bipolar disorder (BD) and major depressive disorder with psychotic features (MDDP), to reflect the real-world diversity of FEP.

For statistical analysis of PANSS and QLS scores, measured prospectively at both time points (FEP and follow-up), DUP and DUI were transformed to quantile variables (Guloksuz et al., 2016; Ferrara et al., 2019; O’Keeffe et al., 2022) with four levels corresponding to their quartiles (DUPQ, DUIQ): Q1 = 1st quartile (containing the lowest 25 % of the data); Q2 = 2nd quartile (containing the lower middle 25 % of the data); Q3 = 3rd quartile (containing the higher middle 25 % of the data); Q4 = 4th quartile (containing the highest 25 % of the data).
Longitudinal trajectory analyses (StataSE 14.2) used mixed-effects models as they utilise all available data, accommodate missing values by avoiding sample bias (from omitting subjects) and estimation bias (from imputation), effectively handle covariates that change over time, and model time effects flexibly, as described previously (Guerguiev and Krystal, 2004; O’Keeffe et al., 2022). An unstructured variance-covariance matrix of the random effects was specified and the restricted maximum likelihood method was used for model fitting. For prediction of PANSS and QLS measures, initial models including DUPQ or DUIQ, together with baseline variables [age at FEP, sex, NART, PAS and length of follow-up], each with a 2-level time variable (FEP and follow-up), were run; non-significant baseline variables were dropped and reduced models for each outcome measure were run, to include any significant baseline variables with DUPQ or DUIQ, time, and DUPQ × time or DUIQ × time interaction terms. Using Stata r.” contrast operator, analysis of any effect of DUPQ or DUIQ involved reference category contrasts, as magnitudes and standard errors (SE), that compared differences between FEP and follow-up and between the 1st quartile and the 2nd, 3rd, and 4th quartiles (O’Keeffe et al., 2022).

For statistical analysis of dysfunction, measured only at follow-up, the four scales evaluated overlapping domains of functionality. Therefore, as described previously in detail (Kingston et al., 2018), principal component analysis (PCA) was applied across these four scales to establish the extent to which they map on to common principle components (PCs); PCA yielded a 4-factor model, with PC1 (hereafter Function1) being the key factor that explained 80.2 % of variance and thus constituted a unitary index that best captures functional evaluation across these four scales. Prediction of Function1 and SES, also measured only at follow-up, by DUPQ or DUIQ was evaluated using statistical techniques analogous to those described above but involving only a single time point. The criterion for statistical significance of all tests was set at p < 0.05.

3. Results

3.1. Demographics

There were 62 subjects [35 male, 27 female: SZ 22 (18 male, 4 female), SF 4 (2 male, 2 female), SA 8 (3 male, 5 female), BD 10 (3 male, 7 female), MDDP 18 (9 male, 9 female); mean age at FEP was 34.1 (SD 18.2) and mean length of follow-up (LFU) was 7.3 (SD 2.8) years; LFU varied with the procedures required for case re-ascertainment in relation to the date at which FEP occurred. Hereafter ‘7-year follow-up’ is used for convenience. Between FEP and 7-year follow-up, clinical management consisted of primarily home-based and community outpatient care under Cavan-Monaghan Mental Health Service, with use of antipsychotic medication supplemented by psychosocial and occupational support as deemed appropriate; there were no intermediate follow-up points between these two occasions. DUP and DUI, together with NART and PAS scores as potential premorbid confounders, are presented in Table 1. As described previously (Nkire et al., 2021a), median DUP and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI and median DUI were shorter than their respective means due to extended upper ranges, indicating right-skewed distributions, with DUI

| Baseline DUP, DUI, NART and PAS assessments. | First psychotic episode |
|---------------------------------------------|------------------------|
| **DUP**                                     | 6.2 (13.0)             |
|                                              | 0.6 (0.0-4.0)          |
|                                              | [0-54]                 |
| **DUI**                                     | 17.9 (47.1)            |
|                                              | 4.4 (1.1-11.9)         |
|                                              | [0-336]                |
| **NART**                                    | 24.9 (9.7)             |
|                                              | 53                     |
| **PAS**                                     | 25.7 (9.4)             |
|                                              | 46                     |

PANSS-P scores at follow-up were lower than at FEP (effect of time in models for both DUPQ and DUIQ, each p < 0.001) (Tables 2a/b and 3a/b) [contrast analyses: follow-up - DUPQ (DUPQ model), -3.7 (0.9), p < 0.001; follow-up - DUPQ (DUPQ model), -4.5 (1.2), p < 0.001]. Both longer DUPQ and longer DUIQ predicted higher PANSS-P symptoms consistently across the study period [effects of DUPQ and DUIQ, each p < 0.01; no DUPQ × time or DUIQ × time interactions] in a manner unrelated to age at FEP, sex or LFU; independently, higher NART (p < 0.05) and lower PAS (p < 0.005) scores also predicted higher PANSS-P scores in the model for DUIQ but not for DUPQ (Table 2a/b). These predictions of PANSS-P scores by DUPQ and DUIQ each derived essentially from the longest quartiles (Table 3a/b) [contrast analyses: DUPQ2 - DUPQ1, -0.6 (1.5); DUPQ3 - DUPQ1, -0.3 (1.4); DUPQ4 - DUPQ1, +4.3 (1.5), p < 0.005; DUIQ2 - DUIQ1, -0.1 (1.7); DUIQ3 - DUIQ1, +0.1 (1.8); DUIQ4 - DUIQ1, +4.58 (1.74), p < 0.01].

PANSS-N scores at follow-up did not differ from those at FEP [no effect of time in models for either DUPQ or DUIQ (Tables 2c/d and 3c/d)]. Both longer DUPQ and longer DUIQ predicted higher PANSS-N scores consistently across the study period [effects of DUPQ and DUIQ, each p < 0.002; no DUPQ × time or DUIQ × time interaction] in a manner unrelated to age at FEP, sex or NART and PAS scores; independently, higher LFU (p < 0.001) also predicted higher PANSS-N scores in the model for DUIQ but not for DUPQ (Table 2c/d). These predictions of PANSS-N scores by DUPQ and DUIQ were each evident in a graded manner across the quartiles (Table 3c/d) [contrast analyses: DUPQ2 - DUPQ1, +0.2 (2.2); DUPQ3 - DUPQ1, +4.4 (2.2), p < 0.05; DUPQ4 - DUPQ1, +7.4 (2.2), p < 0.001; DUIQ2 - DUIQ1, -0.9 (2.3); DUIQ3 - DUIQ1, +4.7 (2.3), p < 0.05; DUIQ4 - DUIQ1, -7.3 (2.3), p < 0.001].

PANSS-G scores at follow-up were lower than at FEP in the model for DUIQ [effect of time, p < 0.05; contrast analysis: follow-up - FEP, -5.5 (2.77), p < 0.05] but not in the model for DUPQ (Tables 2e/f and 3e/f). Both longer DUPQ and longer DUIQ predicted higher PANSS-G scores consistently across the study period [effects of DUPQ and DUIQ, each p < 0.05; no DUPQ × time or DUIQ × time interactions] in a manner unrelated to age at FEP, sex or LFU; independently, higher NART (p < 0.05) and lower PAS (p < 0.005) scores also predicted higher PANSS-G scores in the model for DUIQ but not for DUPQ (Table 2e/f). These predictions by DUPQ and DUIQ each derived essentially from the longest quartiles (Table 3e/f) [contrast analyses: DUPQ2 - DUPQ1, -3.00 (3.2); DUPQ3 - DUPQ1, -2.2 (2.9); DUPQ4 - DUPQ1, +8.4 (2.8), p < 0.005; DUIQ2 - DUIQ1, +0.3 (3.3); DUIQ3 - DUIQ1, +2.1 (3.5); DUIQ4 - DUIQ1, +4.58 (1.74), p < 0.01].
Table 2  
Mixed-effects model analysis for prediction of outcome measures by DUP and DUI at first episode psychosis and 7-year follow-up.

| DUP-outcome measure | χ² (df) | p | DUI-outcome measure | χ² (df) | p |
|---------------------|---------|---|---------------------|---------|---|
| (a) PANSS-P Time    | 18.94   | <0.001 | Time PANSS-P³¹      | 14.53   | <0.001 |
| DUP quartile        | 12.62   | 0.006 | DUP quartile        | 11.42   | 0.010 |
| DUP quartile × time | 7.54    | 0.057 | DUP quartile × time | 5.92    | 0.116 |
| interaction         | (3)     |     | interaction         | (3)     |     |
| (c) PANSS-N Time    | 0.29    | 0.589 | PANSS-N²            | 0.26    | 0.612 |
| DUP quartile        | 15.02   | 0.002 | DUP quartile        | 19.47   | <0.001 |
| DUP quartile × time | 6.90    | 0.075 | DUP quartile × time | 6.27    | 0.099 |
| interaction         | (3)     |     | interaction         | (3)     |     |
| (e) PANSS-G² Time   | 2.40    | 0.121 | PANSS-G²            | 3.95    | 0.047 |
| DUP quartile        | 15.54   | 0.001 | DUP quartile        | 9.69    | 0.021 |
| DUP quartile × time | 3.80    | 0.284 | DUP quartile × time | 4.63    | 0.201 |
| interaction         | (3)     |     | interaction         | (3)     |     |
| (g) QLS² Time       | 4.03    | 0.045 | QLS²                | 2.72    | 0.099 |
| DUP quartile        | 24.85   | <0.001 | DUP quartile        | 28.56   | <0.001 |
| DUP quartile × time | 6.84    | 0.077 | DUP quartile × time | 0.06    | 0.996 |
| interaction         | (3)     |     | interaction         | (3)     |     |

DUP, duration of untreated psychosis; DUI, duration of untreated illness; PANSS, Positive and Negative Syndrome Scale–positive (P), negative (N) and general (G) subscales; QLS, Quality of Life Scale; NART, National Adult Reading Test; PAS, Premorbid Adjustment Scale; LFU, length of follow-up. Significant baseline variables also included in models: ¹ higher PANSS-P also predicted independently by higher NART score (p < 0.05) and lower PAS score (p < 0.005); ² higher PANSS-N also predicted independently by higher LFU (p < 0.001); ³ higher PANSS-G also predicted independently by lower PAS score (p < 0.02); ⁴ higher PANSS-G also predicted independently by higher NART score (p < 0.05) and lower PAS score (p < 0.005); ⁵ lower QLS also predicted independently by longer LFU (p < 0.02); ⁶ lower QLS also predicted independently by longer LFU (p = 0.001).

DUIQ4 - DUIQ1, +8.6 (3.4), p < 0.01.

3.3. Quality of life from FEP to follow-up

QLS scores at follow-up were higher than at FEP in the model for DUPQ (effect of time, p < 0.05; contrast analysis: follow-up - FEP, +8.5 (4.2), p < 0.05) but not in the model for DUIQ (Tables 2g/h and 3g/h). Both longer DUPQ and longer DUIQ predicted lower QLS scores consistently across the study period (effects of DUPQ and DUIQ, each p < 0.05; no DUPQ × time or DUIQ × time interactions) in a manner unrelated to age at FEP, sex, or NART and PAS scores; independently, longer LFU (p < 0.02) also predicted lower QLS scores in the models for both DUPQ and DUIQ (Table 2g/h). These predictions by DUPQ and DUIQ were each evident in a graded manner across the quartiles (Table 3g/h) (contrast analyses: DUPQQ - DQUIQ, +3.2 (8.0); DUPQ3 - DUPQ1, −22.0 (7.4), p < 0.005; DUPQ4 - DUPQ1, −28.8 (7.6), p < 0.001; DUIQ2 - DUIQ1, −5.1 (7.9); DUIQ3 - DUIQ1, −26.1 (8.1), p < 0.001; DUIQ4 - DUIQ1, −36.0 (8.0), p < 0.001).

3.4. Functionality and service engagement at follow-up

Both longer DUPQ [F(3,46) = 3.77, p < 0.02] and longer DUIQ [F(3,44) = 3.04, p < 0.05] predicted lower Function1 at follow-up in a manner unrelated to age at FEP, sex, LFU or NART and PAS scores. These predictions of Function1 by DUPQ (DUPQ1 + 0.25 (0.91), DUPQ2 + 0.36 (0.93), DUPQ3 + 0.06 (0.89), DUPQ4 −0.90 (1.31); contrast analyses: DUPQ4 vs Q1, p < 0.01) and DUIQ (DUIQ1 −0.46 (0.51), DUIQ2 + 0.19 (0.85), DUIQ3 −0.28 (1.21), DUIQ4 −0.77 (1.35); contrast analyses: DUIQ4 vs Q1, p < 0.01) derived essentially from the longest quartiles.

Longer DUPQ [F(3,47) = 3.77, p < 0.02], but not longer DUIQ, predicted higher SES scores at follow-up in a manner unrelated to age at FEP, sex, LFU or NART and PAS scores. This prediction of SES scores by DUPQ [DUPQ1 + 9.5 (10.9), DUPQ2 + 12.1 (12.5), DUPQ3 + 9.5 (10.5), DUPQ4 + 22.7 (12.7); contrast analysis: DUPQ4 vs Q1, p < 0.01] derived essentially from the longest quartile.

4. Discussion

4.1. Overview

In summary: (a) PANSS-P and PANSS-G scores decreased between FEP and 7-year follow-up, while PANSS-N scores did not; (b) Longer DUPQ and DUIQ each predicted higher PANSS-P, PANSS-N and PANSS-G symptom scores consistently across this period; (c) While these effects of longer DUPQ-DUIQ to predict higher PANSS-P and PANSS-G scores were confined essentially to the longest quartile, Q4, their prediction of higher PANSS-N scores was distributed in an ordinal manner across the quartiles; (d) longer DUPQ and DUIQ each predicted lower quality of life consistently across this period and this was also distributed in an ordinal manner across the quartiles; (e) At follow-up, longer DUPQ and DUIQ predicted both lower functionality and lower service engagement, an effect confined essentially to the longest quartile, Q4.

4.2. Relationships to psychopathology and quality of life across 7 years

The length and distribution of DUP in this follow-up cohort are similar to those in the full CAMFEPS dataset at FEP (Nkire et al., 2021a) and are within the wide range identified in previous systematic reviews and meta-analyses on DUP in diagnostically diverse populations (Penttila et al., 2014; Howes et al., 2021). In contrast, while the length and distribution of DUI in this follow-up cohort are also similar to those in the full CAMFEPS dataset at FEP (Nkire et al., 2021a), there is a paucity of comparable systematic data on DUI (Penttila et al., 2014; Clarke et al., 2016; Howes et al., 2021). Thus, the extent and manner in which DUP vis-à-vis DUP might be related similarly or distinctly to the prospective prediction of outcome across the long-term trajectory of psychotic illness from FEP has remained substantially unexplored. Recent meta-analyses of studies at FEP and at a median of 3.0 years post-FEP indicate that DUP predicts severity of psychopathology, more reliably for negative than for positive symptoms (Penttila et al., 2014; Howes et al., 2021), in the absence of data on DUI. The present study shows that longer DUPQ and DUIQ are each associated with higher overall symptom severity (negative > positive > general) in a substantially consistent manner across a 7-year period.

Recent meta-analyses of studies at FEP and at a median of 1.5 years post-FEP indicate that DUP reliably predicts quality of life, (Penttila et al., 2014; Watson et al., 2018; Howes et al., 2021), in the absence of data on DUI. The present study shows that longer DUPQ and DUIQ are each associated with lower quality of life in a substantially consistent manner across a 7-year period. In psychotic illness, quality of life is influenced by multiple factors, particularly negative symptoms (Watson et al., 2018). Therefore, the present relationship between longer DUP-Q and lower quality of life may reflect, at least in part, the relationship between longer DUP-DUI and higher negative symptoms.

DUIQ4 - DUIQ1, +8.6 (3.4), p < 0.01.
4.3. Relationships to functionality and service engagement at 7-year follow-up

Recent meta-analyses of studies at a median of 3.0 years post-FEP indicate that DUP may reflect overall functionality (Penttila et al., 2014; Howes et al., 2021), with relationships between DUP and service engagement and between DUI and either functionality or service engagement not having previously received systematic evaluation. The present study shows that at 7 years post-FEP longer DUPQ and DUIQ predicted both lower functionality and lower service engagement.

Functionality in psychosis reflects the real-world impact of multiple factors that include negative symptoms and cognitive impairment (Harvey and Strassnig, 2012). As on meta-analysis the relationship between DUP and cognition appears to be minimal (Penttila et al., 2014; Howes et al., 2021), the present relationship between longer DUP-DUI and lower functionality may involve, at least in part, the processes that underlie the relationship between longer DUP-DUI and higher negative symptoms. Service engagement is a core aspect of treatment for psychotic diagnoses (Howes et al., 2017; Cheng et al., 2020). On this basis, DUP and DUI would differ only in the numerical sense that DUI constitutes a longer expression of that process than DUP, such that instances where DUI is more reliably associated with a given outcome than DUP may reflect DUI capturing the earlier start and longer duration of that process.

4.5. Quantitative relationships between DUP-DUI gradation and outcome

Whether associations between DUP-DUI are distributed uniformly across the range of values encountered or vary with particular gradations of DUP-DUI within that range remains substantially unknown (Penttila et al., 2014; Howes et al., 2021). In the present study, prediction of higher positive and general symptoms across the 7-year period and of lower functionality and service engagement at 7-year follow-up by longer DUP-DUI was confined to the longest 25 % (Q4) of DUP-DUI values. It appears that the uppermost quartiles of the right-skewed distribution of DUP-DUI within that range remains substantially unknown.

Table 3

| Quartile | FEP | FU | Mean | Quartile | FEP | FU | Mean |
|----------|-----|----|------|----------|-----|----|------|
| (a) PANSS-P | DUPQ1 | 14.1 (5.0) | 9.0 (3.2) | 12.1 (5.0) | DUIQ1 | 15.4 (5.3) | 8.1 (1.7) | 12.6 (5.5) |
| | DUPQ2 | 12.5 (5.3) | 9.1 (3.5) | 10.7 (4.7) | DUIQ2 | 13.3 (6.0) | 9.4 (3.5) | 11.3 (5.1) |
| | DUPQ3 | 14.6 (7.0) | 8.7 (2.2) | 12.0 (6.1) | DUIQ3 | 12.7 (5.8) | 10.3 (5.2) | 11.6 (5.6) |
| | DUPQ4 | 15.9 (5.4) | 16.2 (6.4) | 16.0 (5.8)** | DUIQ4 | 16.3 (5.7) | 14.6 (6.5)** | 15.5 (6.0)** |
| Mean | 14.4 (5.8) | 10.8 (5.1) | 12.7 (5.7) | Mean | 14.4 (5.7) | 10.8 (5.1) | 12.8 (5.7) |
| (c) PANSS-N | DUPQ1 | 12.6 (4.6) | 13.8 (9.7) | 13.0 (7.0) | DUIQ1 | 14.7 (7.3) | 11.9 (6.8) | 13.6 (7.1) |
| | DUPQ2 | 15.1 (9.8) | 10.9 (5.7) | 12.9 (8.0) | DUIQ2 | 15.1 (8.5) | 10.4 (6.0) | 12.8 (6.8) |
| | DUPQ3 | 19.8 (7.3) | 14.6 (7.7) | 17.4 (7.8)* | DUIQ3 | 18.3 (9.6) | 17.8 (11.6) | 18.1 (10.3)* |
| | DUPQ4 | 18.4 (7.6) | 23.1 (11.5) | 20.6 (9.8)** | DUIQ4 | 17.9 (5.0) | 23.2 (10.6) | 20.4 (8.3)** |
| Mean | 16.4 (7.7) | 15.7 (9.8) | 16.1 (8.7) | Mean | 16.6 (7.7) | 15.9 (9.8) | 16.3 (8.8) |
| (e) PANSS-G | DUPQ1 | 29.2 (9.8) | 25.8 (9.3) | 27.8 (9.6) | DUIQ1 | 30.5 (10.6) | 25.6 (6.2) | 28.6 (9.3) |
| | DUPQ2 | 28.4 (10.0) | 26.0 (7.3) | 27.1 (8.6) | DUIQ2 | 30.6 (10.9) | 26.3 (8.5) | 28.3 (9.8) |
| | DUPQ3 | 32.4 (14.2) | 26.7 (6.6) | 29.8 (11.6) | DUIQ3 | 30.2 (15.2) | 29.1 (9.7) | 29.7 (12.8) |
| | DUPQ4 | 32.8 (8.8) | 38.8 (14.5) | 35.7 (12.1)** | DUIQ4 | 31.6 (7.6) | 36.5 (15.1) | 33.9 (11.8)** |
| Mean | 30.8 (11.0) | 29.4 (11.1) | 30.1 (12.1) | Mean | 30.7 (11.1) | 29.5 (11.2) | 30.2 (11.1) |
| (g) QLS | DUPQ1 | 94.0 (19.0) | 93.6 (30.2) | 93.8 (23.6) | DUIQ1 | 94.4 (19.2) | 101.7 (13.7) | 97.3 (17.3) |
| | DUPQ2 | 98.0 (12.9) | 96.3 (22.1) | 97.1 (17.9) | DUIQ2 | 87.5 (21.9) | 95.0 (20.9) | 91.4 (21.3) |
| | DUPQ3 | 58.5 (23.7) | 84.6 (30.2) | 70.9 (29.5)* | DUIQ3 | 68.9 (27.0) | 77.8 (37.5) | 72.8 (31.8)** |
| | DUPQ4 | 59.4 (20.8) | 66.8 (37.0) | 63.1 (29.6)** | DUIQ4 | 58.2 (23.1) | 65.2 (37.1) | 61.7 (30.5)** |
| Mean | 76.9 (26.8) | 84.7 (31.9) | 80.6 (29.4) | Mean | 77.2 (26.7) | 83.9 (32.2) | 80.3 (29.4) |

DUP, duration of untreated psychosis; DUI, duration of untreated illness; PANSS, Positive and Negative Syndrome Scale—positive (P), negative (N) and—general (G) subscales; QLS, Quality of Life Scale; FEP, first episode psychosis; FU, follow-up. Data are mean (SD). *p < 0.05, **p < 0.01, ***p < 0.001 vs DUPQ1 or DUIQ1 and p < 0.05, **p < 0.01 vs FEP are indicative of reference category contrasts; for full details on the direction and magnitude of each reference category contrast (SE) see Results 3.2 and 3.3.
4.6. **Strengths and limitations**

The strengths of the study include its epidemiological representativeness and prospective design, with the same measures of psychopathology and quality of life assessed longitudinally from FEP to 7-year follow-up by the same investigatory team. They extend to evaluation of DUP as well as DUP and consideration of potential confounds. Importantly, mixed-effects models utilise all available data, accommodate missing values by avoiding sample bias and estimation bias, effectively handle covariates that change over time, and model time effects flexibly (Gueorguieva and Krystal, 2004). Furthermore, quantification of DUP-DUI by quantiles is more appropriate and informative for analysis given the non-normal distribution of DUP-DUI values (Guloksuz et al., 2016).

The limitations of the study include lack of assessment of affective symptoms and assessment of functionality and service engagement only at 7-year follow-up. Lack of assessments at intervals between FEP and 7-year follow-up means that the time course of the present relationships between these time points remains unclear. There may be confounds with premorbid features additional to those evaluated. As for the great majority of studies on DUP and outcome, any consequences of the clinical imperative to rapidly initiate long-term treatment with antipsychotic drugs on these relationships remains to be determined.

The definition of DUI for BD and MDDP may be less clear than for SZ: for example, when individuals and informants are asked about first noticeable symptoms in BD and MDDP in the context of FEP, how do their responses relate to that context vis-à-vis a background of depressive symptoms? There is increasing genetic (Brainstorm Consortium, 2018) and neuroimaging (Goodkind et al., 2015; Sheffield et al., 2017; Baker et al., 2018; Ma et al., 2019; Tu et al., 2019; Huang et al., 2020) evidence for overlapping pathobiological processes in SZ, BD and major depressive disorder. Thus, if estimates of DUI are influenced by previous depressive episodes, this may give DUI values relevant to those overlapping pathobiological processes. Our findings show that relationships between DUI and outcome endure across the 7-year prospective period in a manner generally similar to those for DUP. This suggests some mechanistic relationship between DUP and DUI, rather than DUP relating to psychotic features and DUI including also a different relationship to affective features. Future studies should seek to disentangle these issues using larger sample sizes.

5. **Conclusions**

We could not identify any substantive confounding from premorbid features in these relationships from FEP through to 7-year follow-up, in elaboration of systematic investigations at FEP in the full CAMFEPS dataset (Nkire et al., 2021a). However, a recent study (Jonas et al., 2020) has suggested lead-time bias as a variant confound in associations between DUP and outcome measures. While such bias predicts that associations between DUP and outcome should progressively diminish over years post-FEP, in the present study these associations with DUP endured undiminished across seven years post-FEP. Furthermore, associations with DUI, which includes the psychosis prodrome and thus extends the total period of illness back to the emergence of first noticeable symptoms, also endured undiminished across seven years post-FEP. Indeed, such associations with DUP may endure as far as 20 years post-FEP (O’Keeffe et al., 2022). Thus, these findings appear inconsistent with the progressive diminution in associations between DUP and outcome that would be predicted by lead-time bias.

Rather, longer DUP-DUI appears to predict poor outcome in a manner more consistent with enduring psychologically- and/or biologically-based processes associated with DUP and with those prodromal features accessed by DUI. Though CAMFEPS is not an EIS, correlates of the present findings may have implications for EIS: (i) As prediction of poorer outcome by longer DUP-DUI is invariant for at least seven years, this suggests that improvement in outcome through reduction in DUP-DUI may extend for at least a comparable period; (ii) As prediction of negative symptoms-quality of life by longer DUP-DUI is distributed ordinally across the range of DUP-DUI values, while prediction of other domains of outcome appears confined to the longest DUP-DUI values, even modest reductions in DUP-DUI may confer particular advantage in this debilitating and intractable domain of impairment.

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**Declaration of competing interest**

None.

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