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Duration of untreated psychosis and clinical outcomes of first episode psychosis – an observational and an instrumental variables analysis.

Short title: Duration of untreated psychosis and outcomes

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Abstract

Aim

Duration of untreated psychosis (DUP) is considered a key prognostic variable in psychosis. Yet it is unclear whether a longer DUP causes worse outcomes or whether reported associations have alternative explanations.

Methods

Data from two cohorts of patients with first episode psychosis were used (n=2134). Measures of DUP were assessed at baseline and outcomes at 12 months. Regression models were used to investigate associations between DUP and outcomes. We also investigated whether any associations were replicated using instrumental variables analysis to reduce the effect of residual confounding and measurement bias.

Results

There were associations between DUP per 1 year increase and positive psychotic symptoms (7.0% in symptom score increase 95% CI 4.0%,10.0% p<0.001), worse recovery (risk difference (RD) 0.78 95% CI 0.68,0.83 p<0.001) and worse global functioning (0.62 decrease in functioning score 95% CI -1.19,- 0.04 p=0.035). There was no evidence of an association with negative psychotic symptoms (1.0% 95% CI -2.0%,5.0% p=0.455). The instrumental variables analysis showed weaker evidence of associations in the same direction between DUP per 1-year increase and positive psychotic symptoms, recovery and global functioning. However, there was evidence of an inverse association with negative psychotic symptoms (decrease of 15.0% in symptom score 95% CI -26.0% ,-3.0% p=0.016).

Conclusions

We have confirmed previous findings of a positive association between positive psychotic symptoms, global functioning and recovery and DUP using regression analysis. Instrumental variables analysis shows some support for these findings. Future investigation using instrumental variables analysis should be repeated in large datasets.

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Introduction

There is increasing recent interest in the duration of untreated psychosis (DUP - the time-period between the first psychotic symptom appearing and receiving treatment), because there is evidence that it is (positively) associated with poorer outcomes (M. Marshall et al., 2004a; Perkins, Gu, Boteva, & Lieberman, 2005) and is potentially modifiable. However, others have also noted that the relationship is modest (Harrigan, McGorry, & Krstev, 2003) and whether a true association exists has been a matter of intense controversy (T. J. Craig et al., 2000; Ho & Andreasen, 2001). Nonetheless, the apparent prognostic significance of DUP has had a substantial impact on the structure of mental health services in the UK and worldwide (M. Marshall et al., 2004b), resulting in the establishment of designated services with the explicit remit of reducing DUP length and thus hopefully improving clinical outcomes. In the UK this has taken the form of Early Intervention for Psychosis services (Department of Health, 2000), which were initiated circa 2002 and remain in service today in most areas. In short, early intervention for psychosis is considered the most effective and cost-effective approach to the treatment of young people experiencing their first episode of psychosis (FEP) (T. K. Craig et al., 2004). Recent performance targets (National Institute for Clinical Excellence, 2016), driven by the assumption of an association between DUP and outcomes, specify that 50% of people with FEP should have access to a care package within two weeks of referral.

Evidence supporting the existence of independent associations between DUP and clinical outcomes is derived wholly from observational studies and there are several possible methodological explanations for these associations. Mode-of-onset (Warner, 2013) and pre-morbid functioning may confound the association; however, they are often poorly measured or unmeasured. For instance, an insidious mode-of-onset is likely to be associated with a longer DUP because help-seeking is less likely. Whereas, an acute and agitated onset is likely to be associated with a shorter DUP because it is likely to attract the attention of mental health professionals and relevant others involved in the care pathway (Barnes et al., 2000; Larsen, McGlashan, & Moe, 1996). Pre-morbid functioning is also associated with functioning outcome and with DUP because poor functioning is likely to be associated with social isolation, which is associated with a longer DUP (Barnes et al., 2000; Larsen, Johannessen, & Opjordsmoen, 1998; Larsen et al., 1996; Verdoux et al., 1998). DUP is also

challenging to measure accurately, and considerable variability exists in the definition of both the onset and the endpoint (Compton et al., 2007). This is further demonstrated by evidence that the association between DUP and outcomes depends on the definition of the endpoint, with more restrictive definitions resulting in a stronger association (Golay et al., 2016). DUP is also always assessed after entry to care, raising the possibility of recall bias, i.e. the most unwell at initial assessment may recall psychotic symptom onset differently to those less acutely unwell. This is important because symptom severity when commencing treatment is associated with outcomes. Information bias is also possible because few studies have blinded outcome assessors to participants' DUP (Max Marshall et al., 2005). Given these uncertainties it is critical that clinicians have a better understanding of the association between DUP and clinical outcomes, particularly in the current environment of scarce resources and the need for service-commissioning to be based on robust evidence.

Instrumental variables (IV) analysis is designed to overcome some threats to causal inference in observational data, such as residual confounding (confounding by unmeasured or poorly measured variables) and information bias (a systematic error in the measurement of an outcome which is related to the value of the exposure). An IV takes advantage of variable(s) associated with the exposure, but not the outcome (apart from via the exposure) (Munafo & Araya, 2010). IV analysis was first used in economic research and more recently in health research (Davies, Smith, Windmeijer, & Martin, 2013), for instance randomised controlled trials are a special case of IV analysis, where randomisation acts as the instrument. There has been very little IV research in mental health, especially in observational studies, partly because of the difficulty in finding suitable variables for instruments. To qualify as an IV a variable must fulfil three assumptions (Davies, Gunnell, et al., 2013), it must be;

- associated with the exposure
- only associated with the outcome through its effect on the exposure
- not associated with known confounders of the exposure-outcome association (and assumedly unrelated to unknown confounders).

Access to two cohorts of FEP patients, provided an opportunity to investigate the association between DUP and a variety of outcomes using an IV approach.

We set out to investigate whether residual confounding and/or information bias explain most of the apparent association between DUP and clinical outcomes at 12 months in these datasets. If true, there would be no association when an IV was used as a proxy for DUP.

Methods

Sample

National EDEN

National EDEN is a UK-based cohort which aimed to evaluate the implementation and impact of Early

Intervention for Psychosis Teams (EITs) with different configurations throughout England (M.

Birchwood, 2011).

Ethical approval for EDEN was given by Suffolk Local Research Ethics Committee.

MiData

The MiData project evaluated the utility of a computerised audit package for use in seven London

EITs to collect routine data for service-planning, clinical and research purposes (Fisher et al., 2008;

Tseliou et al., 2015).

Wandsworth Research Ethics Committee gave approval for secondary use of the data subject to

complete anonymization.

EDEN and MiData were merged into one dataset for the purposes of these analyses; the total

analysis sample consisted of 2134 participants from 21 EITs.

Data Collection

Outcome Measures at 12 months follow-up

Psychotic symptoms

Data were collected by a research assistant (EDEN) and an EIT clinician (MiData), using the Positive

and Negative Symptom Scale (PANSS) (Kay, Opler, & Lindenmayer, 1989). Inter-rater reliability was

regularly assessed in EDEN (intra-class correlation for psychotic symptoms 0.89-0.91 (Max

Birchwood et al., 2014)). MiData clinicians were trained and expected to reach at least 85%

concordance with expert raters and other team members before completing the measures on their

patients. Assessors were not blinded to DUP in either study.

Recovery

A validated assessment of recovery (Bebbington et al., 2005) was used (EDEN only), by a research

assistant reading medical notes.

Functioning

The Global Assessment of Functioning-Disability Scale (Endicott, Spitzer, Fleiss, & Cohen, 1976) is

designed to be completed by clinicians and was developed from DSM-IV.

Exposure Measure (DUP)

The Nottingham Onset Schedule (NOS) (Singh et al., 2005) was used in both cohorts, although a shortened version was used in MiData. Several DUP components of delay were recorded in EDEN: help-seeking; primary-care; secondary-care mental health services; and the EIT. For the purposes of these analyses the time period of DUP was converted into years and for descriptive analyses dichotomised DUP into 'short' and 'long' (i.e. < or ≥ 6 months (M. Birchwood et al., 2013).

Potential confounders

Age at entry to EIT care and gender. We did not consider diagnosis because, by definition, all patients treated in an EIT are suffering from a psychotic illness.

Statistical analysis

All analyses were carried out using Stata version 13 (StataCorp, 2009).

Data Preparation

PANSS scores were strongly positively skewed (positive symptoms skewness=1.56, negative symptoms skewness=1.53) and therefore the logarithm of each score was used for analysis and back-transformed for presentational purposes.

Analysis 1: Regression

Linear regression was used to investigate the association between DUP and PANSS total positive and negative symptoms score and global functioning at 12 months.

Binomial regression was used to investigate the association between DUP and recovery at 12 months in terms of a risk difference.

Analysis 2: Instrumental Variables (DUPIV)

We selected the mean value of DUP/site (i.e. a variable with 21 values) as the potential instrument. The IV relies on the fact that mean DUP varies across sites due to organisational and local factors, but that this variation is unrelated to patient characteristics or outcomes (except via its effect on individual DUP). More specifically, this instrument is based on the assumption that the characteristics of people presenting to sites with above average DUP will be the same as the characteristics of patients presenting at sites with below average DUP. Similar IV analyses utilising geographic/institutional variation in healthcare exposures have been successfully implemented in other disease areas (Bateman et al., 2013; Bradbury, Do, Winkelmayer, Critchlow, & Brookhart, 2009).

In order to allow a descriptive analysis of demographic variables against DUPIV the variable was dichotomised at a similar distribution point to DUP (see section 2.2.2), which was 10 months.

Stage One
Assumptions testing

We evaluated the association between the DUPIV and DUP using the F-statistic from a least-squares linear regression. We also investigated associations between DUPIV and age and gender, where there should be no or little association. It is not possible to investigate 'back-door' pathways between the IV and the outcomes. This is therefore a theoretical assumption.

Stage Two
IV analysis with each continuous outcome was carried out using the Stata command *ivreg2*. With the binary outcome (recovery) robust standard errors were also used to give a risk difference (Cheung, 2007).

Stage Three
Sensitivity Analyses

1/ Other IVs

We derived four IVs from mean values of DUP components and duration of untreated illness (period of non-psychotic mental illness before entry to EIT). These were mean delay due to; non-psychotic symptoms; psychotic symptoms; EIT (time between first assessment and receiving treatment); and non-psychotic mental illness. This was only possible with EDEN because the shortened version of the NOS DUP used in MiData did not collect data on DUP components. These IV analyses were compared with the findings using DUPIV.

2/ Small sites

Because our IV was based on mean value of DUP/site and there were differences in ethnicity and location between small and large sites we repeated the IV analysis using smaller sites only to investigate biased by site-specific variables.

Results

The four largest sites (Birmingham, Lewisham, Camden and Islington, and Kensington, Chelsea and Westminster) had between 316 and 178 participants, whereas the four smallest (Kings Lynn, East and West Cheshire and Wirral) had between 11 and 27 participants. The largest teams tended to be inner-city with a higher proportion of non-white participants.

Table 1 shows descriptive variables by long and short DUP and DUPIV. Most were male with a mean age of 23 years. Under half were white and 41% had a schizophrenia diagnosis. People with a long DUP were more likely to be white and male. People with a long DUPIV were also more likely to be white and not have a schizophrenia diagnosis.

Analysis 1: Regression analysis (Table 2)

Each year of DUP was associated with an increase in positive PANSS score at follow-up of 7.0%. There was no evidence of an association between DUP and negative PANSS score but every year increase in DUP was associated with a decrease of 22.0% in the probability of full recovery by follow-up. Each increase of one year of DUP was also associated with a 0.6 reduction in global functioning score.

Analysis 2

Stage One - IV Assumptions (Supplementary Table A).

DUPIV was a valid IV since it was strongly associated with DUP but not age or gender (Supplementary Table B and C). The F statistic (evidence against no association between DUPIV and DUP) was also reasonably large (Burgess, 2014). However, Table 1 also shows that DUPIV was associated with potential confounders diagnosis and ethnicity. This provides evidence that it may not be a valid IV.

Stage Two - IV Analysis (Table 3)

The size of the associations with positive PANSS scores and recovery reduced slightly and the 95% CI around the estimates included the null. The association between DUPIV and negative PANSS at 12 months changed in direction and increased. The association between DUP and global functioning increased and changed direction but the 95% CI included negative and null effects. The p value indicates little evidence against the null hypothesis of no association.

Stage Three – Sensitivity Analysis
The findings were mostly materially unchanged (see Supplementary Tables D a-d, E).

Discussion

The regression analyses showed evidence of a small association between longer DUP and worse outcomes in terms of positive psychotic symptoms, recovery and global functioning, but no evidence of an association with negative psychotic symptoms. The IV analysis reduced the size of the associations between positive psychotic symptoms and DUPIV a little and the confidence interval included a null effect. The size of the risk difference between recovery and DUPIV was reduced by 70% and included the null. The association between negative psychotic symptoms and DUPIV increased in size and changed direction suggesting an increase in DUP was associated with a decrease in negative symptoms whereas the association with global functioning score also changed direction and increased in size but the confidence interval included the null. In the results of the analyses which included the null we were not able to exclude the possibility of no association between DUPIV and outcomes.

These findings are at odds with previous research, using standard analyses techniques, which have consistently found an association, and support our hypothesis that some of the association between DUP and outcomes may not be causal but could have alternative explanations.

There are four possible explanations for the differences in findings between IV and standard regression analysis. First, the association between DUP and outcomes may be partly due to measurement bias of the exposure – if someone is very unwell at baseline they or their carer may be more likely to remember a longer period since the emergence of the first psychotic symptom. This is a source of bias because symptom scores at baseline and follow-up are positively associated. Second, residual confounding may account for some/all of the association. The most likely unmeasured confounders are pre-morbid functioning and mode-of-onset (Warner, 2013). It seems likely that poor pre-morbid functioning is associated with longer DUP and a worse outcome (Minor et al., 2015). Mode-of-onset is generally categorised into acute, gradual and insidious (Compton, Chien, Leiner, Goulding, & Weiss, 2008). Acute onset, although traumatic, is associated with better outcomes and a shorter DUP (Compton et al., 2008). Unfortunately, it was not possible to investigate the influence of these variables as the data were not available. However, it is worth noting that individual values of mode-of-onset and pre-morbid functioning *cannot* be associated with mean DUP/site and therefore the use of this variable as an IV will effectively control for confounding by these variables. Thirdly, the

IV was not evenly distributed across categories of ethnicity or diagnosis, which may have introduced a bias. Although it is difficult to predict the effect of this bias, there is some evidence (Ghali et al., 2013; Morgan, Fearon, et al., 2006) that white ethnicity is associated with longer DUP and better outcomes and that people with non-affective psychosis may have longer DUPs and worse outcomes (Heslin et al., 2016; Morgan, Abdul-Al, et al., 2006) than those with affective psychosis.

The IV used is not perfect but, in general, coefficients are in the same direction but attenuated as those estimated by standard regression, which suggests that the standard regression coefficients are inflated by confounding or measurement bias. It is also worth noting that, aside from ethnicity and diagnosis, the IV chosen was effective in balancing the effect of confounders.

The negative psychotic symptoms finding warrants some discussion. Previous research (Max Marshall et al., 2005) has found a positive association between DUP and negative symptoms. We found that each year of DUP is associated with a 15% decrease in negative symptom score. This effect may be an artefact of our sample. High negative symptoms scores are less likely to be a feature of FEP compared to multi-episode psychosis. Therefore, the sub-group with high levels of negative psychotic symptoms may have been unusual in some way which was related to shorter DUP. It is also possible that the lack of training to assess negative psychotic symptoms for assessors in one of our samples (MiData) may have increased measurement error. This finding is difficult to explain but the very small effect size suggests that it may be better to replicate this in a larger sample rather than speculate further.

Strengths and Limitations
The analyses reported here have been conducted on a very large (in the context of psychosis research) naturalistic sample.

We have used a novel statistical approach to reduce the impact of observational data problems such as residual confounding and measurement bias.

The IV was underpowered and this remains a possible explanation for the difference between IV and regression analyses, even though the use of several different instruments in sensitivity analyses resulted in mostly consistent findings. A sample size calculation for the regression analysis suggested that our study was sufficiently powered (at 85%) to detect a 35% difference in positive psychotic symptoms scores between short and long DUP groups as has been found in previous literature

(Drake, Haley, Akhtar, & Lewis, 2000). However, an IV analysis approach requires a much larger sample size for the same statistical power. A power calculation using the statistical software programme R suggested that with a sample size of 1185 (number of participants with psychotic symptoms data at 12 months) we had less than 3% power to detect an association between DUP and positive psychotic symptoms (see Supplementary Material F). Future research in this area should replicate this analysis in larger datasets to improve statistical power and precision.

We also found that DUPIV was associated with ethnicity and diagnosis, which violates one of the IV assumptions and suggests that the IV analysis may suffer from residual confounding.

Deriving instruments from mean values/site is problematic when there is wide variability in site size because size is likely to be related to resources and clinical services, which in turn is likely to be related to mean DUP/site. To investigate this issue, we repeated the analysis including only small sites and the results were materially unchanged. There may also have been neighbourhood characteristics which were associated with DUP and outcomes at each site, but there is evidence that DUP does not vary substantially with neighbourhood (Kirkbride et al., 2010). In preparation for this analysis we also considered other variables which seemed to have potential as an IV, such as distance from service user's home to the treatment centre, but found it was only very weakly associated with DUP and therefore did not fulfil IV criteria.

The follow-up period (12 months) in our study is relatively short and a different pattern of associations may have been found with a longer period.

Clinical Implications

Our regression analyses agree with previous published findings and our IV analyses do not provide strong evidence of a different effect. Therefore, it seems reasonable to conclude that a longer DUP is associated with worse outcomes and that EITs should continue to find ways of reducing DUP. This conclusion requires further triangulation via different methodologies. We also suggest that these findings may imply that the association between DUP and outcomes is complex and that the strength of the association may vary between different service user sub-groups.

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Conflict of Interest Statement
None of the authors have a conflict of interest to declare.

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