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Duration of Untreated Psychosis: Getting Both the Timing and the Sample Right

TO THE EDITOR: In the April 2020 issue of the *Journal*, Jonas et al. (1) reported long-term data on a subgroup from the Suffolk County Mental Health Project naturalistic first-episode psychosis study. In a novel analysis, the duration of untreated psychosis (DUP) predicted trajectory of functioning relative to onset of treatment, consistent with most previous analyses of the effect of DUP (2). Crucially, however, DUP was not predictive when trajectories were defined relative to onset of psychosis. If these results were to generalize to other samples, they would have important implications for early intervention both for the first-episode psychosis and the clinical high-risk paradigms.

We note two reasons, however, that the Jonas et al. findings are unlikely to generalize to other populations. First, the authors limited analyses to the 287 of 628 patients with first-episode psychosis (45.7%) who received schizophrenia spectrum diagnoses at last observation. This post hoc exclusion very likely removed many patients with first-episode psychosis with better functional outcomes, many of whom likely had shorter DUPs, thus biasing the analysis toward the null by design. Indeed, in earlier analyses of this same cohort, the schizophrenia spectrum subgroup of first-episode psychosis patients showed both poorer outcome and longer DUP (3). Second, as described in the accompanying editorial (4), the concept of DUP itself makes most sense when patients receive adequate treatment after the end of the untreated period. Unfortunately, this did not happen here. As the authors note, treatment in this cohort was "intermittent and inconsistent." Viewing the Suffolk County sample as atypical is further supported by a 2005 meta-analysis, in which it was one of only two (from a total of eight) samples not to show a significant effect of DUP on functioning and one of only two (from a total of 14) samples not to show a significant effect on positive symptoms (2).

Jonas et al. have done a conceptual service in pointing out that the association between DUP and illness course can potentially be affected by when the predicted course is selected to begin. We agree that if treatment delay is a modifiable risk factor for outcome, it should predict course relative to psychosis onset as well as course relative to treatment onset. The Jonas et al. sample for testing this possibility, however, is not fit for this purpose. The authors state that their findings require replication, and we agree strongly: their findings should have no policy implications until the DUP prediction of course relative to psychosis onset is investigated in other samples.

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Dr. Woods has received sponsor-initiated research funding support from Amarex, Boehringer-Ingelheim, SyneuRx, and Teva; he has served as a consultant to Boehringer-Ingelheim, the New England Research Institute, and Takeda; he is named as an inventor on a patent for a method of treating prodromal schizophrenia with glycine agonists (U.S. patent 8492418 B2); and he has received royalties from Oxford University Press. Drs. Yung, McGorry, and McGlashan report no financial relationships with commercial interests.

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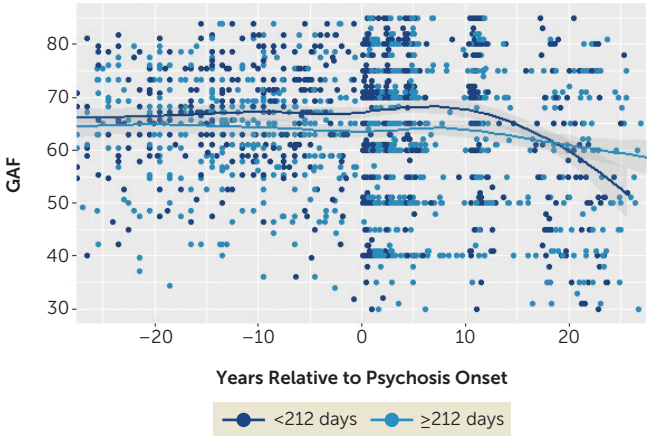
Duration of Untreated Psychosis: Getting Both the Timing and the Sample Right: Response to Woods et al.

TO THE EDITOR: We appreciate the opportunity to read and respond to the insightful letter from Drs. Woods, Yung, McGorry, and McGlashan, leaders in this field of research. They point out two possible confounding effects of our analyses, which concluded that the effect of duration of untreated psychosis (DUP) on long-term outcomes in schizophrenia was explained by lead-time bias. The first point concerns the sample selection, and the second concerns the level of treatment the patients received. We discuss these two points in turn.

Dr. Woods and colleagues note that including only those individuals with a diagnosis of schizophrenia at the last observation could have biased the sample toward poor outcomes. However, we note that the relationship between DUP and outcomes has been largely observed among those with schizophrenia (1–3). Indeed, fitting the same multilevel spline models to data from individuals in the Suffolk

FIGURE 1. LOESS plot of psychosocial function in psychotic disorders other than schizophrenia, as measured by the Global Assessment of Functioning Scale (GAF), as a function of duration of untreated psychosis (DUP) dichotomized at the median of 212 days in a study of the association between DUP and illness course



County Mental Health Project cohort with diagnoses other than schizophrenia found no effect of DUP on either mean psychosocial function or trajectories of psychosocial function. Figure 1 depicts a LOESS plot of trajectories as measured by the Global Assessment of Functioning Scale (GAF) as a function of DUP dichotomized at the median of 212 days, which shows the overlap between these groups.

Second, we note that previous studies of this cohort have documented substantial diagnostic shifts, such that by 24 months after first admission, more than 20% of those diagnosed with schizophrenia shifted into this group from other diagnostic categories (4). By the 10-year follow-up, more than 45% of this group included individuals who had been reassigned from other diagnostic categories (5). As of the 20-year follow-up, this number had reached nearly 50%. Approximately 28% of this group had a baseline diagnosis of other psychotic disorder, while 10% were originally diagnosed with bipolar disorder, 20% with major depressive disorder, and 2% with substance-induced psychosis. For this reason, those with a last available diagnosis of schizophrenia have shorter DUPs (median days, 310) and better baseline psychosocial function (mean GAF score, 52.52) than those with a baseline diagnosis of schizophrenia (median DUP days, 358; mean GAF score, 48.93; both p values <0.01), but not worse outcomes (20-year GAF scores were 52.52 and 48.93, respectively; $p=0.33$). In sum, selecting the sample based on the last available diagnosis captured a group of individuals with diverse initial presentations and a broad range of DUPs and did not create a bias toward poor outcomes.

Dr. Woods and colleagues suggest that halting decline may require interventions more potent than those received by the Suffolk County cohort. The treatment received by this cohort is primarily pharmacological and is not comparable to the vocational rehabilitation, family education, and individual therapy implemented in NAVIGATE (6), OnTrackNY (https://www.ontrackny.org), and a number of other early intervention programs. Such comprehensive coordinated specialty care programs may be more effective—although long-term follow-up of these cohorts is needed.

However, we do not find evidence that the Suffolk County cohort is atypical, as Dr. Woods and colleagues suppose. Before adjustment for lead-time bias, the association between DUP and psychosocial function was moderate in size (Cohen's $d=0.75$, $p<0.001$). Meta-analytic evidence indicates that outcomes in the Suffolk County cohort are consistent with other representative samples with first-admission psychosis (7). Therefore, although the treatment is not equivalent to that received by patients in clinical trials, it is representative of treatment received by patients with first-admission psychosis. As such, this cohort is important for understanding the current state of intervention for schizophrenia in the community.

In sum, we believe that our sample is an informative one in which to evaluate the association between DUP and long-term outcomes. Results support our finding that lead-time bias confounds the association between DUP and illness course in schizophrenia.

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Natural History, Not Lead Time

TO THE EDITOR: In the April 2020 issue of the *Journal*, Jonas et al. analyzed longitudinal data from a sample of individuals with schizophrenia who suffered delayed access (median duration of untreated psychosis [DUP], >300 days) to, and "intermittent and inconsistent" treatment after, a first admission for psychosis. Despite inadequate aftercare, shorter delays from psychosis onset to first admission predicted better outcomes 2 years, but unsurprisingly not 10 or 20 years, later (1). We were thus puzzled with the authors' conclusion: "The association between DUP and psychosocial function may be an artifact of early detection, creating the illusion that early intervention is associated with improved outcomes." We believe this incorrect inference reveals a conceptual confusion about lead-time bias and other sources of bias.

Lead time is usually conceptualized as the interval by which diagnosis is advanced to an earlier point in the natural history of a disease. Such early detection can occur via screening for asymptomatic disease, or proactive case identification of an already manifest illness (2). Lead-time bias is the spurious attribution of benefit to intervention offered early (during the lead time) relative to later (upon usual presentation to care). Textbook examples include the illusory benefit of increased 5-year survival among individuals whose asymptomatic tumors (e.g., lung, breast) were identified earlier by screening programs but who suffered similarly shortened life expectancies as those identified in routine care. For early intervention to meaningfully improve outcomes, the disease must be identifiable at a stage before it is usually recognized, and the ensuing intervention should be more effective when applied earlier in the illness course (2). This has been demonstrated for psychotic disorders: when DUP was successfully reduced and followed with a model of care closer to modern standards, outcomes up to 10 years later were measurably improved compared with samples not exposed to early detection (3). Such prospective and controlled tests of early detection can minimize lead-time bias as well as other important sources of systematic error, such as length-time bias (those who accept intervention may differ in illness duration and prognosis from those who do not) and compliance bias (those who accept intervention may differ prognostically from those who do not) (4).

Observational studies are methodologically more vulnerable to such biases, as they are unable to manipulate the key variable of treatment timing and must rely on data from patients who happen to present for care. Jonas et al. report on a self-selected or convenience sample not subjected to early detection (no lead time was gained, so no such bias can logically ensue) and instead more likely biased in the other ways outlined above. The results are better framed as approximating the natural history of schizophrenia in premodern systems of care, that is, the long-term outcomes of individuals who navigated to a first admission after unacceptably long and likely aversive pathways to care, with which they subsequently engaged only erratically (e.g., self-reported antipsychotic use 25% of the time). More than 2 decades ago, such observations motivated innovations in specialty team–based and youth-oriented care models that have survived experimental, and inferentially stronger, tests of demonstrated improvements in both access (5) and care quality (6). Modern early intervention services that wed these two elements of early detection with comprehensive care now offer the prospect of durable impact (7). Skepticism about such claims should motivate investigators to design studies that can manipulate the relevant variables of timing and treatment quality.

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Natural History, Not Lead Time: Response to Srihari et al.

TO THE EDITOR: We appreciate the opportunity to review the letter from Drs. Srihari, Guloksuz, and Friis, who have contributed much to our understanding of psychosis and