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Utilising symptom dimensions with diagnostic categories improves prediction of time to first remission in first-episode psychosis

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Abstract

There has been much recent debate concerning the relative clinical utility of symptom dimensions versus conventional diagnostic categories in patients with psychosis. We investigated whether symptom dimensions rated at presentation for first-episode psychosis (FEP) better predicted time to first remission than categorical diagnosis over a four-year follow-up. The sample comprised 193 FEP patients aged 18-65 years who presented to psychiatric services in South London, UK, between 2006 and 2010. Psychopathology was assessed at baseline with the Positive and Negative Syndrome Scale and five symptom dimensions were derived using Wallwork/Fortgang's model; baseline diagnoses were grouped using DSM-IV codes. Time to start of first remission was ascertained from clinical records. The Bayesian Information Criterion (BIC) was used to find the best fitting accelerated failure time model of dimensions, diagnoses and time to first remission. Sixty percent of patients remitted over the four years following first presentation to psychiatric services, and the average time to start of first remission was 18.3 weeks (SD=26.0, median=8). The positive (BIC=166.26), excited (BIC=167.30) and disorganised/concrete (BIC=168.77) symptom dimensions, and a diagnosis of schizophrenia (BIC=166.91) predicted time to first remission. However, a combination of the DSM-IV diagnosis of schizophrenia with all five symptom dimensions led to the best fitting model (BIC=164.35). Combining categorical diagnosis with symptom dimension scores in FEP patients improved the accuracy of predicting time to first remission. Thus our data suggest that the decision to consign symptom dimensions to an annexe in DSM-5 should be reconsidered at the earliest opportunity.

*Key words***:** accelerated failure time model; diagnosis; psychosis; remission; schizophrenia; symptom dimensions

1. Introduction

The wide variability in treatment response among patients with first-episode psychosis (FEP) can be understood by viewing psychosis as involving heterogeneous disorders with diverse clinical presentations (Keshavan et al., 2013). Currently, the validity of traditional diagnoses is highly debated (Jablensky, 2016), and their link to the treatment and prognosis of psychotic disorders remains uncertain (Bentall, 2006; van Os et al., 1999). Instead, some postulate that psychosis symptom dimensions may be more useful in providing information about need for care and prognosis (Allardyce et al, 2007; Bakker et al., 2013; Demjaha et al., 2009). Although the ideal number and features of these dimensions is not confirmed, many studies suggest a symptom dimension model comprising five specific constructs (i.e., positive, negative, disorganised, mania, and depression symptoms) (van Os & Reininghaus, 2016). Based on previous work, Wallwork et al. (2012) derived a consensus five-factor model of psychosis that comprised positive (e.g., delusions, hallucinatory behaviour), negative (e.g., blunted affect, emotional withdrawal), disorganised/concrete (e.g., conceptual disorganisation, difficulty in abstract thinking), excited (e.g., excitement, hostility), and depressed (e.g., depression, guilt feeling) dimensions. This Wallwork/Fortgang model of psychosis (Wallwork et al., 2012) has been shown to be the most robust factorial solution for exploring symptom profiles in patients with psychosis (Langeveld et al., 2013); thus we will use this model in the present study.

Remission is one of the most commonly used indicators of treatment efficacy and response in psychosis (Lasser et al., 2007). Although 40-70% of patients with FEP achieve remission at some point over the course of their illness (Austin et al., 2013; Emsley et al., 2006; Lambert et al., 2006; Langeveld et al., 2012), predicting those who will remit, and how long this will take, remains challenging. Previously, age of illness onset and duration of untreated psychosis have been linked to time to remission (Malla et al., 2006), but the influence of symptom dimensions expressed at presentation to services has not yet been investigated in comparison to traditional diagnostic categories.

The DSM-5 schizophrenia panel initially recommended that symptom dimensions should be used to supplement categorical diagnosis but ultimately this view was rejected (van Os, 2015). In the present study, we compared the utility of psychosis symptom dimensions derived using the Wallwork/Fortgang five-factor model (Wallwork et al., 2012) with conventional diagnostic categories to predict time to first remission in a well-characterised sample of patients presenting to psychiatric services for the first time with psychosis. We hypothesised that the symptom dimensions would provide a more accurate prediction of time to first remission than diagnostic categories. Building on previous research which highlighted that combining dimensional measures with categorical diagnoses is more informative than considering them separately (Allardyce et al., 2007), we further tested whether combining symptom dimensions with categorical diagnoses led to a more robust model for predicting time to first remission. As the evidence suggests that the first 3-5 years after first illness onset constitutes a critical period for intervention (Crumlish et al., 2009), we focused on the first four years of illness after first contact with mental health services for psychosis.

2. Methods

2.1. Sample

Participants were recruited as part of the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study conducted in South London, UK. Further details of the sample are available in Di Forti et al. (2014). Briefly, this study included patients aged 18-65 years who presented to psychiatric services of the South London and Maudsley (SLaM) National Health Service (NHS) Mental Health Foundation Trust between December 2006 and October 2010 with a first episode of psychosis (Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV; American Psychiatric Association, 1994). In total, 236 FEP patients were rated on the Positive and

Negative Syndrome Scale (PANSS; Kay et al., 1987); 82% (N=193) of these were successfully traced four years after first contact with mental health services. Therefore, this study involves retrospective analysis of the data collected prospectively for these 193 cases. Ethical permission was obtained from the SLaM and the Institute of Psychiatry Research Ethics Committee. All patients gave informed written consent after reading a detailed information sheet.

2.2. Measures at baseline

2.2.1. Socio-demographic characteristics. Information on socio-demographic characteristics was collated using a modified version of the Medical Research Council (MRC) Socio-demographic Schedule (Mallett et al., 2002). Ethnicity was self-ascribed using the 16 categories employed by the UK Census in 2001 (http://www.ons.gov.uk/ons/guide-method/census/2001/index.html).

2.2.2. Clinical assessments at baseline. Age at first contact was defined as age at which a patient was first in contact with mental health services due to their psychotic symptoms (McKenzie et al., 2001). Duration of untreated psychosis (DUP) was defined as the time between the date of appearance of the first psychotic symptom and the date of treatment with antipsychotic medications (Norman & Malla, 2001). The 30-item PANSS (Kay et al., 1987) was conducted in face-to-face interviews with patients to assess psychotic symptoms over the preceding week. In the present study, researchers underwent comprehensive training in administering the PANSS and had to demonstrate a high degree of comparability in their practice ratings with expert raters. Although not formally tested here, high levels of inter-rater reliability have previously been demonstrated after sufficient training (Kay et al., 1988; Muller & Wetzel, 1998). Baseline diagnoses were derived from interviews and mental health records using the Operational Criteria Checklist for Psychotic Illness (OPCRIT)

(McGuffin et al., 1991). The diagnoses were grouped using DSM-IV codes into schizophrenia (295), schizophreniform disorder (295.40), affective psychoses (296, 296.24, 296.44), schizoaffective disorder (295.70), and other psychoses (297.1, 198.9).

2.3. Tracing patients at follow-up

Approximately 4 years (M=4.4, SD=1.8; 839 person years) after first contact with psychiatric services for psychosis, we sought to trace all 236 FEP cases included in the original GAP study and who had given consent for their clinical records to be accessed at follow-up. The tracing procedure is outlined in Figure 1 and further information provided in Supplementary Materials. During the first four years of follow-up, of all FEP cases, 15 (6.4%) had emigrated, 5 (2.1%) had died, and 7 (3.0%) were excluded as these patients did not have information on follow-up and their contact details were not available at baseline to enable us to trace them either via their GP or ONS/GRO tracing procedures. Those who had died tended to be significantly older at study entry (Supplementary Table 1). We were unable to trace 16 (6.8%) patients via electronic records. Ultimately, we successfully traced 93.2% of our original sample and information on first remission, time to first remission and other variables collected at follow-up was available for 81.8% (N=193/236) of patients.

2.3.1. Measures at 4-year follow-up

Information on outcomes was collated from clinical records using the World Health Organisation (WHO) Life Chart Schedule (LCS) extended version (WHO, 1992). We used this measure at the end of the follow-up period to obtain standardised retrospective assessments of patients' experiences, clinical and social outcomes for the entire period of illness operationalised as the period from the first contact with mental health services for FEP to the date of the last assessment recorded in electronic notes. The LCS measure has

been widely used in prospective and retrospective studies (Ajnakina et al., 2017; Morgan et al., 2014; Schoeler et al., 2017; van Os et al., 1996), and has been shown to be reliable for follow-up assessments and adaptable across cultures (Jablensky et al., 1992, Susser et al., 2000).

2.3.1.1. Clinical assessment at follow-up. Similar to previous research (Morgan et al., 2014) using information extracted from clinical records, first remission was operationalised as the very first continuous period of ≥6 months of a complete absence of a clear record of psychotic symptoms in clinical notes, including no evidence of re-emergence of psychotic symptoms, re-admission to psychiatric wards, and/or having been re-referred to acute home treatment/crisis intervention services during the follow-up period (Ajnakina et al., 2017). This definition did not depend on whether non-psychotic symptoms (e.g. depressed mood, neurotic manifestations) were absent, or whether patients were receiving treatment with antipsychotic medications during this period of remission. This definition of remission has been shown to be as reliable and robust as other definitions of remission in FEP patients available in the literature (Lally et al., in press), including the consensus definition outlined by Andreasen et al. (2005). Time to first remission was defined as the period from the date of first contact with mental health services for FEP to the date of first complete absence of a clear record of psychotic symptoms in clinical notes as indicated above for ≥6 months (Loebel et al., 1992). Those patients who had not remitted at all during the 4-year follow-up period were assigned a value of 208 weeks (i.e., full 4 years) as is customary in survival analysis. Similar to previous reports (Schoeler et al., 2017), adherence to antipsychotic medications over the course of follow-up was assessed on a three-point scale indicating the proportion of time a patient was estimated to be taking antipsychotic medications as prescribed (1: 0-33% of the 4-year period; 2: 34-66%; and 3: 67-100%). Those patients whose psychiatrists advised them to stop taking antipsychotics were defined as fully adherent with this treatment.

2.3.1.2. Social outcomes and drug use. Using the LCS, we collected from the electronic clinical case records information on socio-demographics, such as living arrangements, relationship status, and substance use during the follow-up period.

2.4. Analysis

All tests for analyses described in this section were two-tailed and a $p<0.05$ was considered statistically significant. All analyses were conducted in STATA release 14 (STATA Corp LP, USA).

2.4.1. Confirmatory factor analysis (CFA). CFA was conducted to evaluate the statistical fit (Stefanovics et al., 2014) of the Wallwork/Fortgang's five-factor model of psychosis (Wallwork et al., 2012) in patients with FEP. This model includes positive (P1, P3, P5, G9), negative (N1, N2, N3, N4, N6 and G7), excited (P4, P7, G8 and G14), disorganised/concrete (P2, N5, G11), and depressed (G2, G3, G6) factors. The detailed description of methods employed to conduct CFA using this sample is available in Ajnakina et al (2016) and further information is provided in the Supplementary Materials.

2.4.2. Association analyses and model selection. Because the assumption of proportional hazards for the traditional Cox regression analysis was not regularly met, we chose an accelerated failure time model (AFT) for right censored data. The AFT model assumes that the effect of a covariate is to either accelerate or decelerate the life course of illness by some constant rather than assuming the effect is constant over time (Sastry, 1997). The parameter coefficients in the AFT model were converted into percentage differences in time to first

remission through the equation: ((e^{β} -1) x 100%) (Holtz et al., 2006). This means that the median difference in time to first remission is ((e^{β} -1) x median time to first remission (i.e., 8 weeks)). A more detailed description of the AFT models chosen for the study, their parameters and interpretations of results are provided in Supplementary Table 2 and the Supplementary Materials.

Next using Bayesian Information Criterion (BIC) and ΔBIC scores for each of these models, we compared the performance of all AFT models that included the symptom dimensions and diagnostic categories individually and in combination as predictors of time to first remission. The ΔBIC was defined as the BIC score for the model minus the score for the model with the lowest BIC score (Elderd et al. 2013). Therefore, the best model will have a ΔBIC score of 0. Models >4 units away from the best model (ΔBIC>4) are considered to be significantly inferior (Elderd et al., 2013).

To identify potential confounding variables, we examined variables collected at baseline (i.e., age at first contact with mental health services, relationship and employment status, living arrangements, educational attainments, DUP, and illicit substance use) and during follow-up (i.e., medication adherence, relationship and employment status, living arrangements and illicit substance use) by conducting univariate analysis with time to first remission as the dependent variable. The covariates with $p<0.20$ were considered for our multivariate model. We eliminated the variables with the largest p-values individually until all the remaining variables had $p<0.05$. This procedure highlighted age at first contact, DUP, and illicit substance use during the follow-up period as significant confounding factors. As evidence suggests that medication adherence over the course of follow-up is an important confounding factor for time to remission (Malla et al., 2006), we additionally included this variable in our final analyses.

3. Results

3.1. Patient characteristics

The demographic characteristics of the 193 patients and remission of psychosis over four-year follow-up are presented in Table 1. The mean age at first contact was 28.2 years (SD=98.2); 64.8% of the sample were men; almost two-thirds of the sample had a diagnosis of schizophrenia or schizophreniform disorders; and 34.2% were of White ethnicity, though the largest ethnic group in this sample was of Black ethnicity (39.9%).

3.2. Confirmatory factor analysis

The CFA produced an excellent fit of the model: CFI=0.959, RMSEA=0.052 (90% CI=0.037-0.067) and SRMR=0.071. Patients with a baseline diagnosis of schizophrenia had higher scores on the disorganised/concrete symptom dimension compared with all other diagnostic categories (F=3.60, df=185, *p*=0.001). There were no other significant differences between baseline diagnostic categories on the five symptom dimensions (Figure 2).

3.3. Time to first remission

The rate of remission during the first four years of illness was 59.1% and the average time to the start of the first period of remission was 18.3 weeks (SD=26.0; median=8, IQR=5-20). Those who did not remit (N=76) showed more severe scores on the disorganised/concrete symptom dimension compared to remitters at the time of study entry though this just fell short of statistical significance (t=1.89, df=183, *p*=0.06). There were no other significant differences in symptom dimensions at baseline between remitters and non-remitters.

3.4. Associations between time to first remission and symptom dimensions vs diagnostic categories

Multivariate AFT model estimates of time to first remission over the first four years of follow-up are provided in Table 2. The results showed that a 1-unit increase in the positive symptom dimension measured at baseline was associated with an increase of 8.3% in the time to first remission. Consequently, an increase of 1 unit in the positive symptom dimension corresponds to a median increase of the time to first remission of 4 days. Similarly, 1-unit increase in the excited dimension was associated with an increase of 18.5%, and in the disorganised/concrete dimension was associated with an increase of 4.8% to first remission. An increase of 1-unit in the combined five symptom dimensions corresponds to a median increase of the time to first remission of 7 days. Furthermore, the baseline diagnosis of schizophrenia was significantly associated with an increase of 27.0% of time to first remission compared to non-schizophrenia diagnoses; this entails a median increase of the time to first remission of 2 weeks. Finally, 1-unit increase in the score that combined both the baseline diagnosis of schizophrenia with all five symptom dimensions was associated with an increase of 8.3% of time to first remission, which equates to a median increase of the time to first remission of 4 days.

3.5. Choosing the best model for predicting time to first remission

The results of the BIC and ΔBIC analyses are presented in Table 3. Compared to all five categorical diagnoses singularly (Models 7-11), using symptom dimensions individually as predictors of time to first remission did not result in models with a better performance (Models 1-5). Using all five categorical diagnoses in combination produced a model (Model 12) with an equal performance to the model that combined all five symptom dimensions (Model 6) in predicting time to first remission. Further analyses showed that supplementing baseline diagnosis of schizophrenia with the five symptom dimensions generated the best fitting model (Model 13) for predicting time to first remission. Compared to this best fitting model (Model 13), Models 1, 2, 6, and 7 demonstrated a reasonable (ΔBIC<4) but inferior

(ΔBIC>0) fit to the data. Although Model 9 shows that affective psychosis diagnosis is significantly associated with decreased time to first remission, the results of the BIC and ΔBIC analyses highlight this model has significantly poorer performance compared to the best fitting model (Model 13). Therefore, this model does not perform well enough to warrant validity.

4. Discussion

This is the first longitudinal study to have examined the predictive value of dimensional and diagnostic approaches, both individually and in combination, in predicting and quantifying time to first remission in FEP patients during the initial four years after first contact with psychiatric services. This extends previous work focusing on symptom dimensions and rates of remission in FEP (Emsley et al., 2006, 2007). We found that the positive, excited and disorganised/concrete dimensions of psychosis were important predictors of time to first remission in our sample. In demonstrating this in FEP patients, we have produced an important first step in mapping these putative markers of response onto illness outcome. Not surprisingly, we found that of all diagnostic categories examined in this study schizophrenia was the only one associated with a longer time to first remission. This observation is consistent with a characterisation of this disorder as one with lower rates of remission and a more disabling course than other psychotic disorders (Harrow et al., 2000; Jaaskelainen et al., 2013). However, in contrast to our hypothesis, psychosis symptom dimensions were not superior to the traditional diagnostic categories in predicting time to first remission. In fact, the combination of the baseline diagnosis of schizophrenia with the five symptom dimensions produced the best model fit. This may be because combining a categorical diagnosis of schizophrenia with higher scores on symptom dimensions indexes greater severity of psychotic illness at first presentation to services.

These results also have important implications for the current diagnostic classification systems. There is a growing consensus that the combination of the categorical approach with symptom dimensions allows a more accurate classification of affected individuals into categorical diagnoses based on profiles of specific symptom dimensions (Reininghaus et al., 2013; van Os & Kapur, 2009). The continuous dimension scores further enhance the classification by adding information on the severity of psychopathology (van Os & Reininghaus, 2016). Our findings extend this further by showing that considering the categorical and dimensional approaches together provides greater information about patients' need for care and treatment response after first contact with mental health services. Therefore, our results suggest that it was most unfortunate that symptom dimensions were relegated to an Annexe within DSM-5. This should be reconsidered at the earliest opportunity.

4.1. Strengths

The five-factor model of psychosis symptoms employed in the present study was selected for being a consensus model derived from existing studies (Wallwork et al., 2012) that has been shown to be optimal for use in FEP samples (Langeveld et al., 2013). We have undertaken a thorough approach to data extraction from clinical records and tracing patients, thus ensuring a low level of attrition. Additionally, we employed a definition of remission with demonstrated robust validity and reliability (Lally et al., in press). The symptom dimensions were founded on the PANSS which has previously been shown to be resilient to the effects of age, severity of symptoms, chronicity of illness (White et al., 1997) and short-term medication withdrawal (Lindenmayer et al., 1994). Moreover, the sample utilised in the present study was a well-characterised sample of recent-onset patients presenting for the first time with psychosis and thus the findings are not likely to be confounded by chronicity of illness or prolonged medication use.

4.2. Limitations

Nearly 80% of our patients were recruited from inpatient units; this may imply that very early remitters might not have been fully represented from the start. Follow-up studies tend to suffer from systematic bias due to the non-random loss of information during the follow-up period. Nonetheless, we reduced the risk for this potential bias by establishing the whereabouts, deaths and emigration status for 93% of our sample. It is possible that clinicians might not always have recorded in the electronic notes when symptoms were present and thus in some cases patients may have been classified inaccurately as remitters. Similarly, in some cases inaccuracies in classification may have occurred as electronic notes might not always have contained information on patients' well-being for periods when they were not in contact with mental health services. Nonetheless, it has been shown that it is possible to reliably quantify the course of disorder using routine data from clinical notes (Bebbington et al., 2006). Moreover, our thorough approach to data extraction from clinical notes has ensured that the rates of remission and time to first remission reported in this study are consistent with earlier studies which collected data from face-to-face interviews only (Revier et al., 2015), extracted it retrospectively from clinical notes (Ajnakina et al., 2017; Bromet et al., 2005; Harrison et al., 2001; Kohler et al., 2009) or employed both approaches (Morgan et al., 2014; Schoeler et al., 2017). Many diagnostic categories assigned to patients on first contact with mental health services may either be provisional or likely to change over the illness course (Schwartz et al., 2000), as seen in our sample with a relatively high number of patients with a diagnosis of schizophreniform disorder. Nevertheless, in the present study we focused on the baseline diagnosis, rather than the diagnosis obtained at the end of the follow-up period, to emulate the naturalistic setting for all patients with FEP when predicting time to first remission depending on the diagnosis received at the very first contact with psychiatric services. Finally, it is imperative to investigate the predictive power of our best fitting model in a large independent sample.

Additionally, in this study we specifically focused on symptom dimensions and diagnostic categories but it would be useful for future studies to expand our best fitting model to incorporate a wider range of potential predictors of time to first remission (e.g., see Emsley et al., 2006, 2007).

4.3. Conclusion

Our findings indicate that the use of a combination of five symptom dimensions and the traditional diagnostic classification of psychosis provides a more robust prediction of the length of time that it would take for patients to respond to treatment after the first contact with mental health services for FEP. The results of this study should be replicated in other prospective cohorts with larger samples.

References

Ajnakina, O., Lally, J., Di Forti, M., Kolliakou, A., Gardner-Sood, P., Lopez-Morinigo, J., Dazzan, P., Pariante, C. M., Mondelli, V., MacCabe, J., David, A. S., Gaughran, F., Murray, R. M., Vassos, E. 2017. Patterns of illness and care over the 5 years following onset of psychosis in different ethnic groups; the GAP-5 study. Soc. Psychiatry Psychiatr. Epidemiol. doi:10.1007/s00127-017-1417-6.

Ajnakina, O., Trotta, A., Oakley-Hannibal, E., Di Forti, M., Stilo, S. A., Kolliakou, A., Gardner-Sood, P., Gaughran, F., David, A.S., Dazzan, P., Pariante, C., Mondelli, V., Morgan, C., Vassos, E., Murray, R. M., Fisher, H. L., 2016. Impact of childhood adversities on specific symptom dimensions in first-episode psychosis. Psychol. Med. 46 (2), 317-326.

Allardyce, J., McCreadie, R. G., Morrison, G., van Os, J., 2007. Do symptom dimensions or categorical diagnoses best discriminate between known risk factors for psychosis? Soc. Psychiatry Psychiatr. Epidemiol. 42 (6), 429-437.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders-IV edition. APA, Washington, DC.

Austin, S. F., Mors, O., Secher, R. G., Hjorthøj, C. R., Albert, N., Bertelsen, M., Jensen, H., Jeppesen, P., Petersen, L., Randers, L., Thorup, A., Nordentoft, M., 2013. Predictors of recovery in first episode psychosis: The OPUS cohort at 10year follow-up. Schizophr. Res. 150 (1), 163-168.

Bakker, P. R., Wichers, M., van Harten, P. N., Myin-Germeys, I., Delespaul, P., van Os, J., 2013. Novel directions for psychiatric diagnosis: from psychopathology to motor function to monitoring technology. Epidemiol. Psychiatr. Sci. 22 (4), 289-295.

Bebbington, P. E., Craig, T., Garety, P., Fowler, D., Dunn, G., Colbert, S., Fornells-Ambrojo, M., Kuipers, E., 2006. Remission and relapse in psychosis: operational definitions based on case-note data. Psychol. Med. 36, 1551-62.

Bentall, R., 2006. Madness explained: why we must reject the Kraepelinian paradigm and replace it with a 'complaint-orientated' approach to understanding mental illness. Med. Hypotheses 66 (2), 220-233.

Bromet, E. J., Naz, B., Fochtmann, L. J., Carlson, G. A., Tanenberg-Karant, M. 2005. Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. Schizophr. Bull. 31, 639-649.

Crumlish, N., Whitty, P., Clarke, M., Browne, S., Kamali, M., Gervin, M., McTigue, O., Kinsella, A., Waddington, J.L., Larkin, C., O'Callaghan, E., 2009. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. Br. J. Psychiatry 194 (1), 18-24.

Demjaha, A., Morgan, K., Morgan, C., Landau, S., Dean, K., Reichenberg, A., Sham, P., Fearon, P., Hutchinson, G., Jones, P.B., Murray, R.M., Dazzan, P., 2009. Combining dimensional and categorical representation of psychosis: the way forward for DSM-V and ICD-11? Psychol. Med. 39 (12), 1943-1955.

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A.S., Morgan, C., Stahl, D., Khondoker, M., MacCabe, J.H., Murray, R.M., 2014. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr. Bull. 40 (6), 1509-1517.

Elderd, B. D., Dwyer, G., Dukic, V., 2013. Population-level differences in disease transmission: a Bayesian analysis of multiple smallpox epidemics. Epidemics 5 (3), 146-156.

Emsley, R., Oosthuizen, P. P., Kidd, M., Koen, L., Niehaus, D. J. H., Turner, H. J., 2006. Remission in first-episode psychosis: Predictor variables and symptom improvement patterns. J. Clin. Psychiatry 67 (11), 1707-1712.

Emsley, R., Rabinowitz, J., Medori, R.; Early Psychosis Global Working Group, 2007. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. Schizophr. Res. 89 (1-3), 129-139.

Harrison, G., Hopper, K., Craig, T., Laska, E., Siegel, C., Wanderling, J., Dube, K. C., Ganev, K., Giel, R., An Der Heiden, W., Holmberg, S. K., Janca, A., Lee, P. W. H., León, C. A., Malhotra, S., Marsella, A. J., Nakane, Y., Sartorius, N., Shen, Y., Skoda, C., Thara, R., Tsirkin, S. J., Varma, V. K., Walsh, D., Wiersma, D. 2001. Recovery from psychotic illness: A 15- and 25-year international follow-up study. Br. J. Psychiatry 178, 506-517.

Harrow, M., Grossman, L. S., Herbener, E. S., Davies, E. W., 2000. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. Br. J. Psychiatry 177, 421-426.

Holtz, T. H., Sternberg, M., Kammerer, S., Laserson, K. F., Riekstina, V., Zarovska, E., Skripconoka, V., Wells, C.D., Leimane, V., 2006. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann. Intern. Med. 144 (9), 650-659.

Jaaskelainen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., Veijola, J., Miettunen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr. Bull. 39 (6), 1296-1306.

Jablensky, A., 2016. Psychiatric classifications: validity and utility. World Psychiatry 15 (1), 26-31.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J. E., Day, R., Bertelsen, A., 1992. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol. Med. Monogr. Suppl. 20, 1-97.

Kay, S. R., Fiszbein, A., Opler, L. A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261-276.

Kay, S. R., Opler, L. A., Lindenmayer, J. P. 1988. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 23, 99-110.

Keshavan, M. S., Clementz, B. A., Pearlson, G. D., Sweeney, J. A., Tamminga, C. A., 2013. Reimagining psychoses: an agnostic approach to diagnosis. Schizophr. Res. 146, 10-16.

Kohler, S., van der Werf, M., Hart, B., Morrison, G., McCreadie, R., Kirkpatrick, B., Verkaaik, M., Krabbendam, L., Verhey, F., van Os, J., Allardyce, J. 2009. Evidence that better outcome of psychosis in women is reversed with increasing age of onset: a population-based 5-year follow-up study. Schizophr. Res. 113, 226-32.

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K., Gaughran, F., Murray, R. in press. Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long term outcome studies. Br. J. Psychiatry.

Lambert, M., Schimmelmann, B. G., Naber, D., Schacht, A., Karow, A., Wagner, T., Czekalla, J., 2006. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. J. Clin. Psychiatry 67 (11), 1690-1697.

Langeveld, J., Andreassen, O. A., Auestad, B., Faerden, A., Hauge, L. J., Joa, I., Johannessen, J.O., Melle, I., Rund, B.R., Røssberg, J.I., Simonsen, E., Vaglum, P., Larsen, T.K., 2013. Is there an optimal factor structure of the Positive and Negative Syndrome Scale in patients with first-episode psychosis? Scand. J. Psychol. 54 (2), 160-165.

Langeveld, J., Joa, I., Friis, S., Ten Velden Hegelstad, W., Melle, I., Johannessen, J. O., Opjordsmoen, S., Simonsen, E., Vaglum, P., Auestad, B., McGlashan, T., Larsen, T.K., 2012. A comparison of adolescent- and adult-onset first-episode, non-affective psychosis: 2-year follow-up. Eur. Arch. Psychiatry Clin. Neurosci. 262 (7), 599-605.

Lasser, R. A., Nasrallah, H., Helldin, L., Peuskens, J., Kane, J., Docherty, J., Tronco, A.T., 2007. Remission in schizophrenia: applying recent consensus criteria to refine the concept. Schizophr. Res. 96 (1-3), 223-231.

Lindenmayer, J. P., Bernstein-Hyman, R., Grochowski, S., 1994. Five-factor model of schizophrenia. Initial validation. J. Nerv. Ment. Dis. 182 (11), 631-638.

Loebel, A. D., Lieberman, J. A., Alvir, J. M., Mayerhoff, D. I., Geisler, S. H., Szymanski, S. R., 1992. Duration of psychosis and outcome in first-episode schizophrenia. Am. J. Psychiatry 149 (9), 1183-1188.

Malla, A., Norman, R., Schmitz, N., Manchanda, R., Bechard-Evans, L., Takhar, J., Haricharan, R., 2006. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol. Med. 36 (5), 649-658.

Mallett, R., Leff, J., Bhugra, D., Pang, D., Zhao, J. H., 2002. Social environment, ethnicity and schizophrenia. A case-control study. Soc. Psychiatry Psychiatr. Epidemiol. 37 (7), 329-335.

McGuffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system: Arch. Gen. Psychiatry 48 (8), 764-770.

McKenzie, K., Samele, C., Van Horn, E., Tattan, T., Van Os, J., Murray, R., 2001. Comparison of the outcome and treatment of psychosis in people of Caribbean origin living in the UK and British Whites. Report from the UK700 trial. Br. J. Psychiatry 178, 160-165.

Morgan, C., Lappin, J., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., Onyejiaka, A., Croudace, T., Jones, P.B., Murray, R.M., Fearon, P., Doody, G.A., Dazzan, P., 2014. Reappraising the long-term course and outcome of psychotic disorders: The AESOP-10 study. Psychol. Med. 44 (13), 2713-2726.

Muller, M. J., Wetzel, H. 1998. Improvement of inter-rater reliability of PANSS items and subscales by a standardized rater training. Acta Psychiatr. Scand. 98, 135-139.

Norman, R. M., Malla, A. K., 2001. Duration of untreated psychosis: a critical examination of the concept and its importance. Psychol. Med. 31 (3), 381-400.

Reininghaus, U., Priebe, S., Bentall, R. P., 2013. Testing the psychopathology of psychosis: evidence for a general psychosis dimension. Schizophr. Bull. 39 (4), 884-895.

Revier, C. J., Reininghaus, U., Dutta, R., Fearon, P., Murray, R. M., Doody, G. A., Croudace, T., Dazzan, P., Heslin, M., Onyejiaka, A., Kravariti, E., Lappin, J., Lomas, B., Kirkbride, J.B.,

Donoghue, K., Morgan, C., Jones, P.B., 2015. Ten-year outcomes of first-episode psychoses in the MRC AESOP-10 study. J. Nerv. Ment. Dis. 203 (5), 379-386.

Sastry, N., 1997. A nested frailty model for survival data, with an application to the study of child survival in northeast Brazil. J. Am. Stat. Assoc. 92 (438), 426-435.

Schoeler, T., N. Petros, Di Forti, M., Klamerus, E., Foglia, E., Murray, R., Bhattacharyya, S. 2017. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry doi:10.1016/S2215-0366(17)30233-X.

Schwartz, J. E., Fennig, S., Tanenberg-Karant, M., Carlson, G., Craig, T., Galambos, N., Lavelle, J., Bromet, E.J., 2000. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch. Gen. Psychiatry 57 (6), 593-600.

Stefanovics, E. A., Elkis, H., Zhening, L., Zhang, X. Y., Rosenheck, R. A., 2014. A cross-national factor analytic comparison of three models of PANSS symptoms in schizophrenia. Psychiatry Res. 219 (2), 283-289.

Susser, E., Finnerty, M., Mojtabai, R., Yale, S., Conover, S., Goetz, R., Amador, X., 2000. Reliability of the life chart schedule for assessment of the long-term course of schizophrenia. Schizophr. Res. 42 (1), 67-77.

van Os, J., 2015. The transdiagnostic dimension of psychosis: implications for psychiatric nosology and research. Shanghai Arch. Psychiatry, 27 (2), 82-86.

van Os, J., Fahy, T. A., Jones, P., Harvey, I., Sham, P., Lewis, S., Bebbington, P., Toone, B., Williams, M. & Murray, R. 1996. Psychopathological syndromes in the functional psychoses: associations with course and outcome. Psychol Med 26, 161-76.

van Os, J., Gilvarry, C., Bale, R., Van Horn, E., Tattan, T., White, I., Murray, R., 1999. A comparison of the utility of dimensional and categorical representations of psychosis. UK700 Group. Psychol. Med. 29 (3), 595-606.

van Os, J., Kapur, S., 2009. Schizophrenia. Lancet 374 (9690), 635-645.

van Os, J., Reininghaus, U., 2016. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 15 (2), 118-124.

Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr. Res. 137 (1-3), 246-250.

White, L., Harvey, P. D., Opler, L., Lindenmayer, J. P., 1997. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathol 30 (5), 263-274.

World Health Organisation, 1992. The Life Chart Schedule. Developed by Ezra Susser, Sarah Conover, Carole Siegel and an International Team of WHO Investigators. Geneva.

Figure Legends

Figure 1. Flow chart documenting how psychosis patients were traced and administrative outcomes four years after first contact with mental health services for a first episode of psychosis (FEP).

Figure 2. Five psychosis symptom dimension mean scores by traditional diagnostic categories. Graphs display the mean psychosis symptom dimension scores for first-episode psychosis patients with a DSM-IV diagnosis of schizophrenia, affective psychosis, schizophreniform disorder, schizoaffective psychosis, and other psychoses at first presentation to psychiatric services (double-headed lines indicate standard deviations). The continuous symptom dimension scores were derived using the 'predict' post-estimation command in Stata following a confirmatory factor analysis of the Wallwork/Fortgang five-factor model (Wallwork et al., 2012) of the items from the Positive and Negative Syndrome Scale. The five dimensions capture positive, negative, disorganised/concrete, excited, and depressed symptom items at first presentation to psychiatric services for psychosis

***p<0.001

Table 1. *Sample characteristics at baseline and remission of psychosis over four-year follow-up from first presentation to mental health services*

Baseline sample characteristics and remission at follow-up	Total sample N=193
	Mean (SD) / n (%)
Age $_{years}$	28.2 (8.2)
Range	18-60
Gender	
Female	68 (35.2)
Male	125 (64.8)
Ethnicity	
White (all groups)	66 (34.2)
Black (all groups)	77 (39.9)
Other	50 (25.9)
Diagnosis	
Schizophrenia	55 (28.5)
Schizophreniform	52 (28.5)
Affective psychoses	44 (22.8)
Schizoaffective psychosis	26 (13.5)
Other psychoses	16 (8.3)
On antipsychotic medication at study entry	184 (96.3)
DUP $_{days}$	35.0 (118.6)
Years of follow-up	4.4 (1.8)
Median (IQR)	4 (3-5)
Rate of remission	110 (59.1)
Time to first remission $_{weeks}$	18.3 (26.0)
Median (IQR)	8 (5-20)

DUP, duration of untreated psychosis. IQR, Interquartile range. SD, standard deviation.

Table 2. *Multivariate Accelerated Failure Time model estimating difference in time to the start of first remission after first contact with mental health services for psychosis*

Clinical characteristics at first contact	β (SE)	95% CI	*p*-value	β converted to percentage of time to first remission
Symptom dimensions				
Positive	0.08 (0.03)	0.02-0.13	0.008	8.3
Excited	0.17 (0.07)	0.03-0.30	0.014	18.5
Negative	0.01 (0.04)	-0.08-0.09	0.888	1.0
Disorganised/Concrete	0.10 (0.04)	0.01-0.19	0.033	4.8
Depressed	-0.04 (0.07)	-0.18-0.10	0.600	-3.9
All 5 psychosis dimensions	0.12 (0.05)	0.03-0.21	0.008	27.1
Diagnostic categories				
Schizophrenia	0.24 (0.09)	0.06-0.43	0.011	27.0
Schizophreniform disorder	-0.05 (0.08)	-0.22-0.12	0.560	-4.9
Affective psychoses	-0.21 (0.09)	-0.36-0.02	0.026	-18.9
Schizoaffective psychoses	-0.04 (0.11)	-0.26-0.18	0.710	-3.9
Other psychoses	0.13 (0.18)	-0.22-0.49	0.455	13.8
All five diagnostic categories	0.05 (0.03)	-0.01-0.11	0.119	5.1
Combination of both approaches				
Schizophrenia diagnosis and all 5 psychosis dimensions	0.08 (0.03)	0.03-0.13	0.003	8.3

Effect size is indicated by β coefficient and standard error (SE) from the accelerated failure time survival model. CI, confidence interval.
All analyses adjusted for age at the time of first contact with mental health services for psychosis, duration of untreated psychosis, substance use measured during the four-year follow-up period, and antipsychotic medication adherence over the course of follow-up. The β coefficients in the AFT model were converted into percentage differences in time to first remission through the equation: $((e^{\beta} -1) \times 100\%)$ (Holtz et al., 2006).

Table 3. *Comparisons of the fit of all significant models using BIC scores and ΔBIC*

Models	Predictors of time to first remission	BIC	∆BIC
Symptom dimensions			
Model 1	Positive dimension	166.26	1.91
Model 2	Excited dimension	167.30	2.95
Model 3	Negative	173.39	9.04
Model 4	Disorganised/Concrete	168.77	4.42
Model 5	Depressed	173.14	8.79
Model 6	All 5 psychosis dimensions	166.36	2.01
Diagnostic categories			
Model 7	Schizophrenia	166.91	2.56
Model 8	Schizophreniform disorder	173.08	8.73
Model 9	Affective Psychoses	169.03	4.68
Model 10	Schizoaffective psychoses	173.27	8.92
Model 11	Other psychoses	172.83	8.48
Model 12	All five diagnostic categories	171.13	6.78
Combination of both approaches			
Model 13	**Schizophrenia diagnosis and all 5 psychosis dimensions**	**164.35**	0

BIC, Bayesian Information Criterion; ΔBIC is defined as the relevant model minus the model with the lowest BIC score. All models are adjusted for age at the time of first contact with mental health services for psychosis, duration of untreated psychosis, substance use measured during the four-year follow-up period, and antipsychotic medication adherence over the course of follow-up. The model in bold provides the best fit (i.e., the lowest BIC score).

Figure 1
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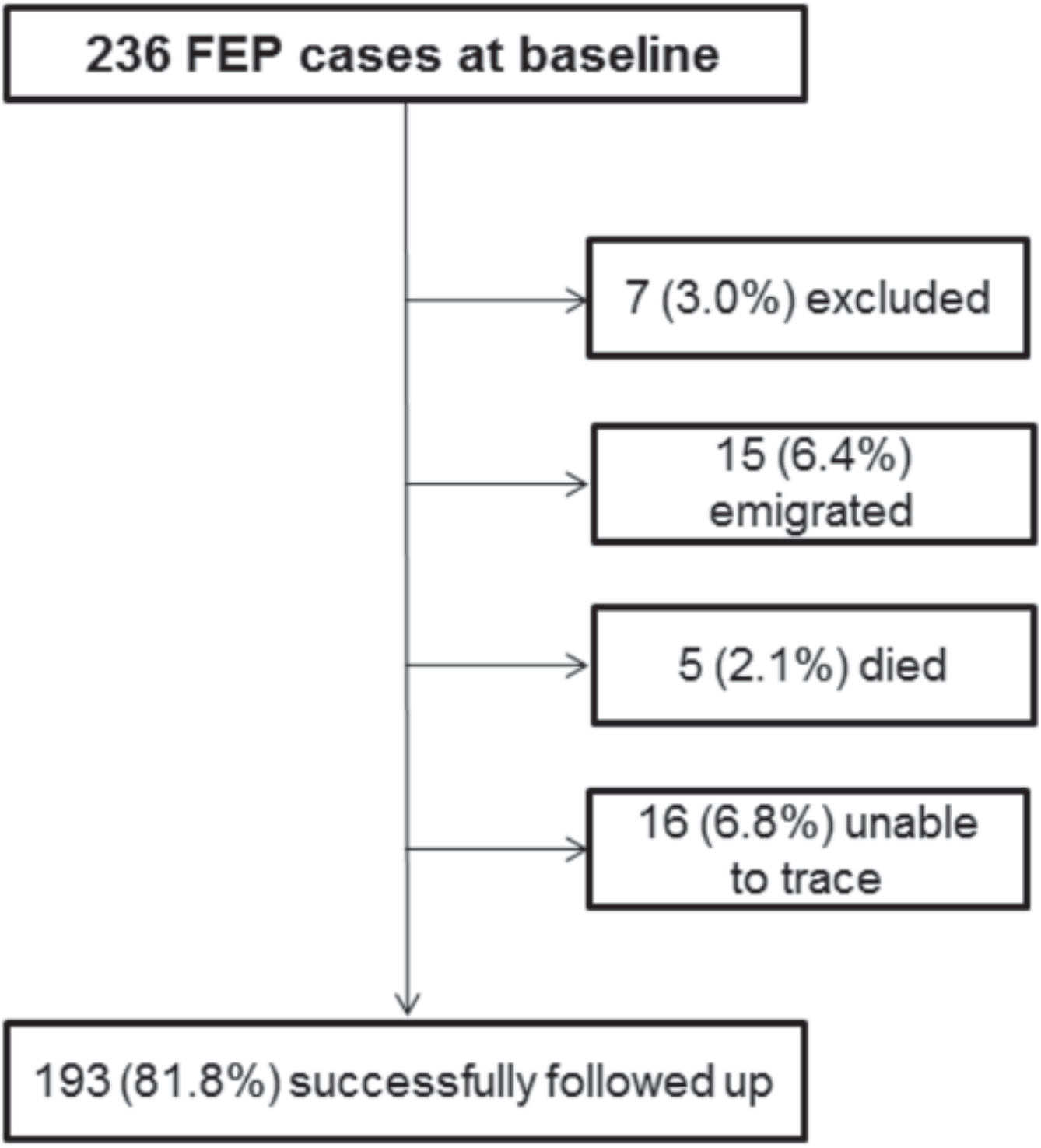

Figure 2

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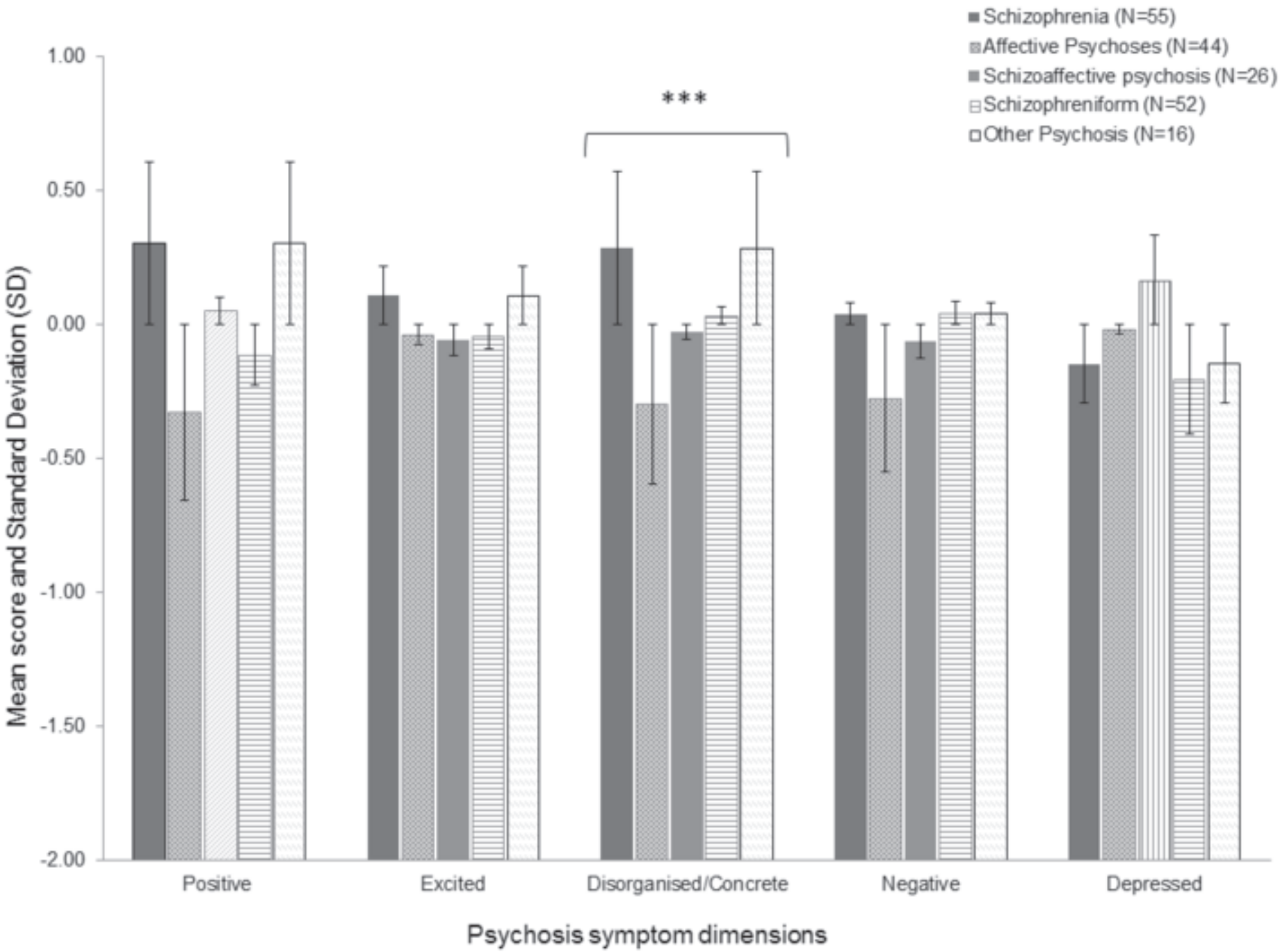

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Conflict of Interest

R.M.M. has received honoraria from Janssen, Astra-Zeneca, Lilly, and BMS. A.S.D. has received honoraria from Janssen and Roche Pharmaceuticals. F.G. has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, Otsuka and Sunovion and has a family member with professional links to Lilly and GSK.

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