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Title: Insight and risk of suicidal behaviour in two first-episode psychosis cohorts: effects of previous suicide attempts and depression

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Keywords: Insight; suicidal behaviour risk; first-episode psychosis; depression

Corresponding Author: Dr. Javier-David Lopez-Morinigo, MBBS PhD

Corresponding Author's Institution: Department of Psychosis Studies. Institute of Psychiatry, Psychology and Neuroscience. King's College London

First Author: Javier-David Lopez-Morinigo, MBBS PhD

Order of Authors: Javier-David Lopez-Morinigo, MBBS PhD; Marta Di Forti, MBBS PhD; Olesja Ajnakina, PhD; Benjamin DR Wiffen, PhD; Kevin Morgan, PhD; Gillian A Doody, BSc MD MRPsych MSc MPhil MMedSci; Peter B Jones, FMedSci, Professor of Psychiatry; Rosa Ayesa-Arriola, PhD; Manuel Canal-Rivero, MSc PhD; Benedicto Crespo-Facorro, MBBS PhD; Robin M Murray, FRS; Paola Dazzan, MD MSc PhD FRCPsych; Craig Morgan; Rina Dutta, MBBS PhD; Anthony S David, MD MSc FRCPsych

Abstract: Background:
The role of insight dimensions - illness recognition (IR), symptoms relabelling (SR), treatment compliance (TC) - in suicide risk in first-episode psychosis (FEP) remains unclear.
Method:
The AESOP (n=181) and GAP (n=112) FEP cohorts were followed-up over 10- and 5 years. Survival analysis modelled time to first suicidal event in relation to baseline scores on the Schedule for the Assessment of Insight, whilst adjusting for demographic, clinical, psychopathological and neuropsychological variables.
Results:
AESOP: those with previous suicide attempts scored higher on IR (7.6±1.9 vs. 5.9±3.0, p<0.01) and total insight scores (TIS) (17.2±5.0 vs. 13.4±6.7, p=0.03). IR (r=0.23, p<0.01), SR (r=0.18, p=0.04) and TC (r=0.26, p<0.01) correlated with depression. Univariable analyses: IR (HR=1.14, 95%CI=0.98-1.34, p=0.09), TC (HR=1.30, 95%CI=0.99-1.71, p=0.06) and TIS (HR=1.06, 95%CI=0.99-1.13, p=0.08) were linked with suicidal behaviour. Multivariable regression models: depression (HR=1.55, 95%CI=1.22-1.97, p<0.01) predicted suicidal behaviour.
GAP: SR (6.4±3.1 vs. 4.5±3.4, p=0.03) and TIS (16.8±6.4 vs. 12.8±7.4, p=0.03) were higher in those with suicidal antecedents. IR (r=0.32, p<0.01) and SR (r=0.27, p=0.01) correlated with depression. Univariable analyses: TC (HR=1.36, 95%CI=1.01-1.83, p=0.04) and TIS (HR=1.06, 95%CI=0.99-1.14, p=0.08) were associated with suicidal behaviour. Multivariable regression models: previous suicide attempts (HR 5.17,

95%CI 1.32-20.29, p=0.02) and depression (HR 1.16, 95%CI=1.00-1.35, p=0.04) predicted suicidal behaviour.
Conclusions:
Suicide attempts prior to FEP and depression at that point were associated with baseline insight levels and predicted risk of suicidal behaviour over the follow-up, which was not linked with insight. This may explain the apparent association of insight with suicidality in FEP.

14th August 2018

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Firstly, we much appreciate your consideration for the publication of our manuscript in Schizophrenia Research.

In response to the reviewers' comments we have introduced the relevant changes in the revised manuscript (using yellow highlighting) and we would like to make the following clarifications:

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Finally, reviewer 1 made a point on the causal pathways linking insight with suicidal behavior, which could be rather different between subjects with different diagnoses, compliance with treatment and socio-cultural aspects (see Belvederi Murri Schizophr Bull. 2018 Jun 23. doi: 10.1093/schbul/sby092). Unfortunately, either the study was underpowered to test this (for example, differences across diagnoses) or we did not collect data on the mentioned variables (e.g. cultural aspects). Accordingly, we have reported this limitation in the revised manuscript (section 4.5., page 15).

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1 King's College London. Institute of Psychiatry, Psychology and Neuroscience. Department of Psychosis Studies (London, UK)

2 King's College London. Institute of Psychiatry, Psychology and Neuroscience. Department of Psychological Medicine (London, UK)

3 Department of Psychology, University of Westminster. (London, UK)

4 Division of Psychiatry. University of Nottingham. (Nottingham, UK)

5 Department of Psychiatry, University of Cambridge. (Cambridge, UK)

6 Department of Psychiatry, Marqués de Valdecilla University Hospital, IDIVAL. School of Medicine, University of Cantabria, Santander, Spain. CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Spain

7 Child and Adolescent Psychiatry and Psychology Department of Hospital Sant Joan de Déu of Barcelona, Spain

8 National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, UK

9 Centre for Epidemiology and Public Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London, UK

a these two authors contributed equally to this work and they should be named conjointly as last authors

*** Corresponding author:**

Javier-David Lopez-Morinigo

Department of Psychosis Studies

PO Box 68. Institute of Psychiatry, Psychology and Neuroscience King's College London.

De Crespigny Park.

London.

SE5 8AF

United Kingdom.

Tel: +44 (0)207 848 5137

Email: javier.lopez-morinigo@kcl.ac.uk

ABSTRACT

Background:

The role of insight dimensions – illness recognition (IR), symptoms relabelling (SR), treatment compliance (TC) - in suicide risk in first-episode psychosis (FEP) remains unclear.

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The AESOP (n=181) and GAP (n=112) FEP cohorts were followed-up over 10- and 5 years. Survival analysis modelled time to first suicidal event in relation to baseline scores on the Schedule for the Assessment of Insight, whilst adjusting for demographic, clinical, psychopathological and neuropsychological variables.

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Conclusions:

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Key words: insight, suicidal behaviour risk, first-episode psychosis, depression.

1. INTRODUCTION

Suicide represents a major contributor to the excess mortality in schizophrenia (Brown, 1997; Saha et al., 2007), with a lifetime suicide rate currently estimated at approximately 5% (Palmer et al., 2005). Between 20% (Lopez-Morinigo et al., 2016) and 40% of patients receiving mental healthcare who take their lives have a psychotic disorder (Lopez-Morinigo et al., 2018). The risk is particularly higher in first-episode of psychosis (FEP) (Melle et al., 2006; Dutta et al., 2010; Dutta et al., 2012; Palmer et al., 2005; Ayesa-Arriola et al., 2015). A previous meta-analysis revealed previous depression and suicide attempts, drugs misuse, agitation or motor restlessness, fear of mental disintegration and poor medication compliance to be the most relevant suicide risk factors in schizophrenia (Hawton et al., 2005). Interestingly, this meta-analysis found a two-fold increased odds of suicide among those with good insight, albeit the number of studies (5) and total number of subjects (N=436) were small and the estimate consequently imprecise (OR=2.04, 95%CI 0.54-7.74); this noted, the OR is consistent with a later meta-analysis of FEP studies (Challis et al., 2013) showing a modest relationship between insight and suicide risk (OR=1.64, 95%CI 1.23-2.56).

Insight in psychosis had not received much attention until it was proposed that it comprised three different, albeit overlapping dimensions – (i) illness recognition, (ii) symptoms relabelling, and (iii) treatment compliance (David, 1990), and measurement scales were devised for research. This multidimensional model of insight was supported by further research (Amador and David, 2004).

Insight in psychosis is of major clinical relevance given its associations with positive outcomes (greater insight, better outcomes) (McEvoy et al., 2004; Lincoln et al., 2007). However, insight is also linked with depression (Mintz et al., 2003), i.e., the 'Insight Paradox' (Lysaker et al., 2007; Belvederi et al., 2015). Indeed, a common assertion among clinicians is that insight in psychosis leads to depression and an increased suicide risk in psychosis, which is known as the 'demoralization syndrome' (Drake et al., 1985; Drake & Cotton, 1986), although this remains unproved (Restifo et al., 2009).

In addition, treatment compliance reduced suicide risk in psychosis (Hawton et al., 2005; Qin et al., 2006). Hence, insight, which is linked with compliance (McEvoy, 2004), may reduce suicide risk via improved compliance. Moreover, recent longitudinal studies either find no relationship between insight and suicide risk in FEP (Ayesa-Arriola et al., 2015) and some reports even suggest that gaining insight may reduce the risk (Bourgeois et al., 2004;

Barrett et al., 2015). From a multidimensional approach to insight, poor compliance was reported to increase risk of suicide in schizophrenia (Hawton et al., 2005), which is in line with a recent meta-analysis which failed to link treatment compliance with depression (Belvederi et al., 2015).

Our previous systematic review looking at insight and suicide risk in schizophrenia and related disorders showed no clear pattern (Lopez-Morinigo et al., 2012). We suggested up to four non-mutually exclusive explanations underlying this, namely selection and recall biases, which affects cross-sectional studies, the use of uni- vs multidimensional insight scales and the extent to which other confounders were considered (Lopez-Morinigo et al., 2012). Indeed, our previous cross-sectional FEP study (Lopez-Morinigo et al., 2014a) demonstrated that suicidal behaviours before first presentation with psychosis, which is the strongest predictor of future suicidal acts (Hawton et al., 2005; Pompili et al., 2011), affected insight levels at that time (Lopez-Morinigo et al., 2014a). Thus, previous cross-sectional studies linking insight with suicidal events were probably missing the more direct association between previous and current suicidal behaviour (Lopez-Morinigo et al., 2012).

We used two large FEP cohorts who were followed-up over prolonged periods to investigate the relationships between suicide attempts prior to first contact with services, baseline variables, including insight and depression, and future suicidal events. We hypothesised that: i) no insight dimension will 'directly' increase suicide risk; ii) previous suicide attempts and depression will be linked with both baseline insight levels and risk of suicidal behaviour; and iii) treatment compliance will 'directly' reduce suicide risk.

2. METHODS

2.1. Participants

We designed an observational prospective cohort study. Data were collected from two FEP projects, namely the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) and the National Institute of Health Research Biomedical Research Centre (NIHR BRC) Genetics and Psychosis (GAP). All incident FEP (F10-F29 and F30-F33 ICD-10 codes (WHO, 1993)) cases presenting to the South London and Maudsley NHS Foundation Trust (London, UK) over 1997-1999 (AESOP) (Morgan et al., 2006) and 2004-2010 (GAP) (Di Forti et al., 2009) were invited to take part in the studies, although a small AESOP subsample came from Nottingham (UK). Organic psychosis, drug-induced psychosis, IQ less than 50 and poor fluency of English were exclusion criteria. Diagnoses were made at study inception, hence they did not take into account any changes over the follow-up period. Participants gave written informed consent and both AESOP and GAP projects received ethical approval from the Local Research Ethics Committees.

2.2. Measures

2.2.1. Premorbid, sociodemographic and clinical variables

We collected data on sex, age at admission (GAP) or first contact with services (AESOP), education level, living status, employment status and cannabis and alcohol use (present/absent). In the AESOP study, the duration of untreated psychosis (DUP) was defined as the time from the first psychotic symptom to first contact with services, while the Nottingham Onset Schedule (Singh et al., 2005) estimated DUP in the GAP sample, i.e., time from first continuous psychotic symptom to treatment onset.

2.2.2. Information on suicidal behaviour over the follow-up

Researchers made phone calls and sent letters to patient's home address and to the general practitioner (GP) at 5- (GAP) or 10 years (AESOP) (Morgan et al., 2014) to invite them to participate in the follow-up studies. Information on suicidal behaviour - which was defined as 'any potentially self-injurious behaviour for which the person intended to kill himself/herself' (O'Carroll et al., 1996), (i.e., non-suicidal self-injuries were not considered (Grandclerc et al., 2016) - was collected from clinical records. Also, AESOP and GAP were linked with national mortality data, namely the Office for National Statistics (ONS), which records the official cause of death (as ICD-10 codes (WHO, 1993)) in England and Wales.

2.2.3. Insight assessment

Insight was evaluated by the Schedule for Assessment of Insight – Expanded version (SAI-E) (Kemp & David, 1997), which takes the form of a semi-structured interview and provided scores on David's model's insight dimensions - 'illness recognition' (IR), 'symptoms relabelling' (SR) and 'treatment compliance' (TC) – and total insight scores (TIS) (higher score, greater insight). The SAI-E was reported to be easily administered in clinical practice (Sanz et al., 1998). The scale author (ASD) provided training for researchers, which resulted in good to excellent inter-rater reliability (for TIS intraclass correlation coefficients ranged from 0.92 to 0.98 ($p<0.001$) (Morgan et al., 2010a)).

2.2.4. Psychopathological symptoms

In order to measure psychopathological symptoms severity, the Positive and Negative Symptoms Scale for Schizophrenia (PANSS, Kay et al., 1987) was used in the GAP study. In line with a systematic review of PANSS factor analyses (Wallwork et al., 2012), five symptomatic dimensions were considered: positive (range: 4-23), negative (range: 6-27), disorganization (range: 3-15), mania (range: 4-16) and depression (range: 3-16), which was specifically measured with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992), ranging from 0 to 24. The AESOP study evaluated psychopathology with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)'s Item Group Checklist (IGC) algorithm (WHO, 1992) and a factor analysis with an overlapping AESOP sample had revealed the above five symptomatic dimensions (Demjaha et al., 2009), with scores ranging from 0 to: 11 (positive), 8 (negative), 4 (disorganization), 10 (mania) and 6 (depression).

2.2.5. Neurocognitive tests

Two overall measures of general cognition were taken: premorbid IQ, which was estimated by the National Adult Reading Test (NART) (Nelson & Willison, 1991), and current IQ, which was assessed by the short version of the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler, 1981). The Trail Making Test (time to complete task B minus time to complete task A) (TMT B-A) (Reitan, 1958) provided a measure of executive functions.

2.3. Statistical analysis

First, we investigated differences in demographic and clinical variables, including insight scores, between patients with/without suicidal history. Second, we conducted

univariable survival analyses to model time from first contact to the first suicidal event (irrespective of outcome) or the censoring date, i.e. either the date on which the patient was last known to be alive or the end of the follow-up study period, whichever came first. Third, those variables associated with first suicide attempt at p≤0.1 were added to multivariable Cox Regression (Cox, 1972) models (enter method) to test the effect of insight scores on time to suicidal event, whilst controlling for confounders. We calculated Hazards Ratios (HRs) of time to event and 95% confidence intervals (CI). We used the Statistical Package for Social Science version 25.0 (SPSS Inc., Chicago, IL, USA).

3. RESULTS

3.1. Baseline differences between patients with/without previous suicide attempts

The baseline characteristics of the samples and differences between those with/without previous suicide attempts are presented in Table 1 (AESOP, n=181) and Table 2 (GAP, n=112).

With regard to insight, in the AESOP cohort (Table 1) those subjects with previous suicide attempts scored higher on IR (7.6±1.9 vs. 5.9±3.0, t=3.1, p<0.01), SR (5.5±3.3 vs. 4.7 ±3.7, t=0.82, p=0.41), TC (4.0±1.4 vs. 3.2±1.5, t=1.9, p=0.05) and TIS (17.2±5.0 vs. 13.4±6.7, t=2.1, p=0.03) than non-suicide attempters. These results were replicated in the GAP sample, in which IR (6.2±2.7 vs. 4.7±3.3, t=2.0, p=0.05), SR (6.4±3.1 vs. 4.5 ±3.4, t=2.2, p=0.03), TC (4.3±1.8 vs. 3.6±1.8, t=1.6, p=0.11) and TIS (16.8±6.4 vs. 12.8±7.4, t=2.2, p=0.03) were higher in suicide attempters than in non-suicide attempters.

In terms of psychopathology, only depression in the AESOP cohort was associated with previous suicide attempts (scores medians in attempters vs. non-attempters: 5.0 vs. 0.0, p<0.01). There were some correlations between psychopathological dimensions and insight scores, which are shown in Table S1 (AESOP) and Table S2 (GAP) of the supplementary material. In both samples depression strongly correlated with all insight scores except compliance in the GAP cohort (r=0.18-0.32) (Table S1 and Table S2).

No neurocognitive differences between those with/without previous suicide attempts emerged from the analyses (Table 1 and Table 2).

Insert Table 1 here

Insert Table 2 here

3.2. Suicidal events over the follow-up

In the AESOP cohort, thirty-four subjects (18.7%) attempted suicide either prior to first presentation or over the follow-up. Sixteen subjects (8.8%) had previous suicide attempts. Twenty-six subjects (14.4%) attempted to end their lives over the follow-up, including eight re-attempters (4.4%), i.e., they attempted suicide before and after first presentation. We compared the 26 follow-up suicide attempters, including 5 suicide completers (hence, a case fatality (CF) of 5/181=2.7%), with 155 non-suicide attempters.

Thirty-two GAP patients (28.5%) attempted suicide either prior to first contact with services or over the study follow-up. Over the follow-up there were 18 suicide attempters (16.1%) and 8 of these (7.1%) did so both before and after first contact with services, including 3 suicides (CF=3/181=2.7%). We therefore compared 18 follow-up suicide attempters and 94 non-suicide attempters.

In total, over the follow-up periods there were 44 suicide attempters and 80 suicidal events. The most common suicide methods were poisoning (n=31) and jumping (n=12), which included jumping off a height or in front of a vehicle. See Table S3 (supplementary material) for details.

In terms of attrition, 11 AESOP patients (6.0%) and 9 GAP subjects (8.0%) were lost to follow-up. We compared these subjects with those who had follow-up data available. There were no differences in age, gender, education level, marital status, living status, employment status, history of previous suicide attempts, diagnoses, drugs/alcohol use, DUP, psychopathological, neurocognitive or insight variables, although in the AESOP cohort the proprotion of Black people was higher in those who could not be followed-up (69.2%) in comparison with follow-up patients (31.2%) (X^2=7.72, p=0.005) and in the GAP cohort those who were lost to follow-up had higher scores on the PANSS positive dimension (p=0.02) than follow-up patients. Data available upon request.

3.3. Risk factors for suicidal behaviour over the follow-up

Univariable analyses of demographic, clinical, psychopathological, neurocognitive and insight variables are shown in Table 3 and Table 4.

Insert Table 3 here

Insert Table 4 here

In the AESOP cohort, previous suicide attempts (HR=2.92, 95%CI=0.96-8.86, p=0.06), executive functions (TMT B-A) (HR=1.01, 95%CI=1.00-1.02, p=0.01), depression (HR=1.57, 95%CI=1.30-1.89, p<0.01), TC (HR=1.30, 95%CI=0.99-1.71, p=0.06) and TIS (HR=1.06, 95%=CI 0.99-1.13, p=0.08) - were linked with time to first suicidal event and were added to a Cox regression model. Depression (HR=1.55, 95%CI=1.22-1.97, p<0.01) and previous suicide attempts (HR=2.75, 95%CI=0.90-8.52, p=0.07) remained associated with time to first suicidal event (Table 5).

In the GAP study, age at first presentation (HR=2.92, 95%CI=0.96-8.86, p=0.06), living alone (HR=3.57, 95%CI=1.32-9.65, p=0.01), previous suicide attempts (HR=3.95, 95% CI=1.55-10.1, p<0.01), premorbid IQ (HR=0.96, 95%CI=0.91-1.01, p=0.09), depression (HR=1.09, 95%CI=0.99-1.08, p=0.08), TC (HR=1.06, 95%CI=1.01-1.83, p=0.04) and TIS (HR=1.06, 95%CI=0.99-1.14, p=0.08) were associated with time to first suicidal event. Age at first presentation, living status, previous suicide attempts, full premorbid IQ, depression, TC and TIS were entered into the Cox regression model. Previous suicide attempts (HR=5.17, 95%CI=1.32-20.29, p=0.02) and depression (HR=1.16, 95%CI=1.00-1.35, p=0.04) remained associated with time to first suicidal event (Table 5).

Insert Table 5 here

These results were replicated when removing depression from the analyses. In particular, in the AESOP cohort previous suicide attempts (HR=4.67, 95%CI=1.65-13.28, p=0.04) and TMT-B-A (HR=1.01, 95%CI=1.00-1.01, p=0.03) were associated with time to first suicidal event, while insight scores failed to replicate such an association. In the GAP cohort, however, living alone (HR=4.50, 95%CI=1.31-15.50, p=0.02) and previous suicide attempts (HR=5.35, 95%CI=1.56-18.32, p<0.01) were linked with time to suicidal behaviour. Similarly, when not including those individuals with previous suicide attempts in the analyses, insight dimensions were not associated with suicidal behaviour. Specifically, in the AESOP cohort only depression (HR=2.45, 95%CI=1.05-5.74), p=0.04) was associated with time to first suicidal act, whilst in the GAP sample these were not significant (p<0.05) predictors of suicidal behaviour.

4. DISCUSSION

4.1. Main findings

In light of our results, we can draw four main conclusions. First, previous suicide attempts and depression were associated with an increased risk of suicidal behaviour in early psychosis. Second, consistent with the first hypothesis, no insight dimension was 'directly' associated with an increased risk of suicidal behaviours, which was predicted by both depression and previous suicide attempts, both of which were linked with baseline insight levels, hence in line with hypothesis ii. In other words, we found no evidence to support the commonly held theory of association between insight and suicide risk in psychosis, which appears to be explained by two confounders, namely, previous suicide attempts and depression. Thirdly, contrary to hypothesis iii, treatment compliance increased risk of suicidal behaviour, although such an association did not remain significant after controlling for confounders. Fourth, our previous finding from the GAP cohort (Lopez-Morinigo et al., 2014a) that suicidal antecedents prior to first presentation influenced insight levels at that point was replicated in the AESOP cohort, consistent with a previous AESOP study with an overlapping sample (Harvey et al., 2008).

4.2. Insight dimensions and risk of suicidal behaviour

Interestingly, insight scores were not associated with suicide risk in the multivariable regression models, which was consistent with our hypotheses, our previous literature review (Lopez-Morinigo et al., 2012) and recent studies (Yan et al., 2013; Pijnenborg et al., 2013; Barrett et al., 2015). Hence, other confounders appear to play a role in the relationship between insight and suicide risk in psychosis, although many clinicians remain concerned about improving insight in early onset psychosis patients.

Gaining awareness of having a psychotic illness could be thought to lead to more severe depressive symptoms, hence increasing the risk of suicide, i.e., the so-called 'demoralization syndrome' (Drake et al., 1985; Drake and Cotton, 1986; Amador et al., 1996; Restifo et al., 2009). However, the 'depressive realism model' may explain why a more depressed patient, who is biased by the cognitive distortions associated with depression (or less prone to 'normal' optimistic biases), tends to think more pessimistically about him/herself (Ghaemi and Rosenquist, 2004), hence being scored higher at the time of the insight assessment. In keeping with this, it could be argued that those with higher levels of insight may be more likely to recall previous suicidal events. This is why in our previous systematic review cited in the introduction (Lopez-Morinigo et al., 2012) we postulated that

recall bias may contribute to the conflicting findings regarding the association between insight and suicide risk in psychosis. Furthermore, although almost half of suicide completers had communicated suicide intent to some extent, it remains unclear what predicts suicide risk in relation to suicide communication, including diagnosis (for instance, psychosis) (Pompili et al., 2016). In order to solve this 'chicken and egg' dilemma, longitudinal intervention studies are needed; for example, if an insight improving intervention was demonstrated not to increase suicidality, this would go against the demoralization syndrome account. This is indeed what intervention studies show (Bourgeois et al., 2004; Pijnenborg et al., 2013; Barretet al., 2015). Specifically, based on the relationship between lack of insight and metacognitive deficits in schizophrenia and related disorders, metacognitive training (MCT) has been postulated to improve insight, which may also decrease suicide risk, although this remains to be established (Lysaker et al., 2018). On the other hand, some insight improving interventions may increase suicide risk. Hence, further research in this area is warranted.

However, treatment compliance increased risk of suicidal behaviour in our both FEP cohorts, which goes against previous reviews (Hawton et al., 2005) and our expectations. From a conceptual point of view, it should be noted that 'awareness' of the need for treatment is not the same as 'acceptance' (Morgan and David, 2010b), which implies some degree of 'subordination', a well-known contributing factor for depression in psychosis (Upthegrove et al., 2016). Also, it could be speculated that the extent to which treatment is successful (in someone who is aware of the need for treatment) may moderate this association, which needs further longitudinal studies. Specifically, our study could not test whether longer-term 'treatment compliance' was linked with greater (or lower) suicide risk.

4.3. Predictors of suicidal behaviour over the follow-up

Younger age at first presentation, living alone, previous suicidal history, executive dysfunction and depression were found to be the four main predictors of suicidal behaviour, in addition to awareness of the need for treatment. However, only previous suicide attempts and depression remained 'significant' (at $p<0.05$) in the final multivariable models. Given their association with insight scores at baseline, previous suicide attempts and depression appear to act as confounders in the relationship between insight and future suicidal behaviours, as discussed below.

Suicide risk in psychosis has been consistently found to be higher in young patients (e.g. Palmer et al., 2005; Limosin et al., 2007; Osborn et al., 2008; Alaräisänen et al., 2009;

Dutta et al., 2010; Barrett et al., 2010a; Barrett et al., 2010b), which was replicated by our results. Hence, early psychosis patients require close monitoring (Popovic et al., 2014; NCISH, 2017). However, it remains unclear whether early intervention services are associated with a decreased suicide risk. Specifically, the initial protective effect seems to disappear once the early intervention period ends (Bertelsen et al., 2008; Melle et al., 2006; Harris et al., 2008), although extending the treatment period reduced suicide rates in Hong Kong when compared with standard care (Chan et al., 2018).

Living alone was linked with an increased suicide risk both in schizophrenia (Hawton et al., 2005) and FEP (Challis et al., 2013). Of concern, most patients with psychosis who reside in our catchment area live alone (Kirkbride et al., 2006). However, to our knowledge no previous studies have tested whether sheltered or supported accommodation in early psychosis may reduce suicide risk.

Overall, conflicting findings have been reported regarding the relationship between neurocognition and suicide risk in psychosis (Andersson et al., 2008, Webb et al., 2011; Potkin et al., 2003; Barrett et al., 2011; Hor & Taylor, 2010), although cognitive impairment may behave as a protective factor in schizophrenia (De Hert et al., 2001). Hence, cohort studies, including comprehensive neurocognitive assessments over time, are warranted in this area.

4.4. Previous suicide attempts and depression were related to baseline insight and predicted future suicidal behaviours

In our previous cross-sectional study with the GAP sample (Lopez-Morinigo et al., 2014a) we demonstrated that suicide attempts preceding first contact with services on affected insight levels at that time, which was replicated by the AESOP sample presented in this study. In addition, previous suicide attempts was associated with an increased risk of future suicidal events in both cohorts, which was in line with previous literature (e.g. De Hert et al., 2001; Hawton et al., 2005; Dutta et al., 2010; Bakst et al., 2010; Pompili et al., 2011) including a 2013 meta-analysis (Challis et al., 2013). Hence, previous suicide attempts (prior to first contact) influenced insight levels at that point. Also, previous suicide attempts, but not baseline insight scores, were associated with suicidal behaviours in the multivariable models, with 'significant' (at $p<0.05$) HRs ranging from 2.75 (AESOP) to 5.31 (GAP), hence a strong association. In other words, previous suicide attempts seem to explain in part the apparent association between insight and suicidal behaviour in psychosis, which is

consistent with a previous cross-sectional study (Massons et al., 2017). Nevertheless, up to 42% of suicide completers with schizophrenia spectrum disorder have no previous suicide attempts (LopezMorinigo et al., 2014b; Lopez-Morinigo et al., 2016).

In addition, depression emerged as the main therapeutic target to prevent suicidality in both FEP cohorts, which was in full agreement with previous literature (Altamura et al., 2003; Bertelsen et al., 2007; Flanagan and Compton, 2012; Harvey et al., 2008; Kontaxakis et al., 2004; Barrett et al., 2010a; Barrett et al., 2010b). Depression was associated with all insight dimensions in both cohorts except compliance in the GAP sample (Lopez-Morinigo et al., 2014a), which is in full agreement with previous literature (Mintz et al., 2003; Belvederi et al., 2015). Hence, depression was associated with insight, and depression, but not insight, remained associated with suicidal behaviours in the multivariable regression models, with 'significant' (at $p<0.05$) HRs ranging from 1.16 (GAP) to 1.55 (AESOP), which was still a strong association since depression was a continuous variable. Hence, depression emerged as the second main confounder explaining the apparent relationship between insight and suicidality in psychosis, consistent with two previous cross-sectional studies (Massons et al., 2017; Roux et al., 2018).

Interestingly, depression was found to be a significant risk factor for suicide, even after adjusting for confounders, in three studies (Bakst et al., 2009; Barrett et al., 2010; Restifo et al., 2009) included in our systematic review (Lopez-Morinigo et al., 2012). These studies had failed to link insight with suicidality, which was predicted by hopelessness (Kim et al., 2003; Bourgeois et al., 2004; Acosta et al., 2009), consistent with a previous meta-analysis (Hawton et al., 2005). Hopelessness, i.e., 'the cognitive element of negative expectations' (Minkoff et al., 1973), was reported to increase suicide risk in outpatients (Beck et al., 1990), thus becoming the main clinical target for suicide risk management in schizophrenia (Pompili et al., 2004).

However, 'depression' in psychosis could be viewed as a symptomatic dimension (Peralta et al., 2013) or a psychological reaction to such a stigmatising diagnosis (Drake & Cotton, 1986). A 1-year follow-up FEP study reported depression in the acute stage to be associated with hearing malevolent voices, use of safety behaviour and subordination to persecutors, while loss, shame, low level continuing positive symptoms and longer duration of untreated psychosis predicted post-psychotic depression (Upthegrove et al., 2014).

Also, prodromal depression was linked with later suicidality and depression in FEP (Upthegrove et al., 2010), which goes against the 'demoralization syndrome' (Drake and

Cotton, 1986), i.e., depression in psychosis appears to have trait-like properties (Upthegrove et al., 2010). However, depression in schizophrenia was demonstrated to have both state- and trait-like properties, both of which were different from negative symptoms (Chiappelli et al., 2014). Indeed, distinguishing negative symptoms from depression remains challenging in the clinical setting, which has relevant clinical implications since overall, depression is a major contributor for suicide in schizophrenia (Hawton et al., 2005) and FEP (Pompili et al., 2011; Challis et al., 2013; McGinty et al., 2017). However, current guidelines in the treatment of depression in patients with schizophrenia are limited (Gregory et al., 2017).

In summary, three points should be carefully considered in future studies addressing this issue. First, previous suicide attempts behave as the strongest predictor of future suicidal events both in schizophrenia (e.g. Hawton et al., 2005) and FEP (Challis et al., 2013) and previous suicide attempts influence insight levels at first presentations with psychosis (Lopez-Morinigo et al., 2014a). Second, depression in psychosis, which has both state- and trait-like properties (Chiappelli et al., 2014) and can precede the onset of psychotic symptoms, is linked with previous and future suicidal acts and insight levels at the time of assessment (i.e. at first contact with services). Therefore, prospective intervention studies such as randomized clinical trials comparing those receiving an intervention aimed at improving both insight and depression with those without such treatment may shed some light on this issue; for instance, by comparing those receiving MCT (Lysaker et al., 2018) vs. those with standard care. In particular, these studies should carefully assess depressive symptom severity, insight levels and suicide risk over time and from a statistical point of view mediation analyses should be performed.

4.5. Strengths and limitations

This is the first longitudinal study testing the role of multiple insight dimensions in suicidal behaviour in early psychosis. In addition, two large FEP cohorts were followed-up over prolonged periods. All incident FEP cases presenting to NHS hospitals in the catchment areas were approached and invited to take part in the studies. Since most psychosis patients in the UK receive NHS-funded mental healthcare, the samples are likely to be representative. A number of demographic, clinical, psychopathological, insight-related and neurocognitive variables were comprehensively assessed using validated instruments. Also, the low attrition rates (6-8%), with no relevant differences between those who were

lost to follow-up and those who were not (see section 3.2. above for details), are unlikely to have affected the findings significantly.

However, this study has several limitations. First, the samples may have been underpowered to detect some between-groups differences. This was likely to apply to those who took their lives (in total, only 8 subjects in this study). As a result, we could not analyse the relationship between lethality and suicide methods (among other variables) in FEP patients. Second, other variables such as premorbid personality (Lysaker et al., 1999; Campos et al., 2011; Cuesta et al., 2011; Ritsner & Blumenkrantz, 2010), premorbid adjustment (Keshavan et al., 2004) and neuroanatomical correlates (Morgan et al., 2010a; David et al., 2012), which were not evaluated in this study, may contribute to insight. Third, researchers were not blind to other assessments which might affect the insight scores (Campos et al., 2011). Fourth, we could not investigate insight changes over time (Wiffen et al., 2010; Campos et al., 2011; Cuesta et al., 2011; AyesaArriola et al., 2014), which were only evaluated in a small AESOP subsample, in relation to suicide risk. Fifth, diagnoses were made at the study inception, which may have resulted in the inclusion of patients who may have transitioned to a non-psychotic diagnosis over the follow-up, although this is unlikely given the diagnosis stability of psychotic disorders (Heslin et al., 2015). In addition, diagnoses and other variables such as treatment compliance and socio-cultural issues, which were not evaluated in this study, may have affected the relationship between insight and suicide risk (Belvederi Murri & Amore, 2018).

4.6. Final remarks

We followed-up two large FEP cohorts over prolonged periods to investigate the role of insight in suicide risk in early psychosis; however, we found no evidence of a 'direct' association of insight with suicidal behaviour. Specifically, previous suicide attempts and depression emerged as the main predictors of suicidal behaviour and they were linked with baseline insight levels. However, insight scores were not associated with suicidal behaviour in the multivariable regression models, i.e., after controlling for confounders. Also, these findings were replicated when removing depression from the analyses and when those subjects with previous suicide attempts were not included in the models, which provides further support for the confounding role of both previous suicide attempts and depression in the relationship between insight and suicidality in psychosis. This seems to explain the clinical notion that insight increases risk of suicidal behaviour in psychosis, in line with two previous cross-sectional studies (Massons et al., 2017; Roux et al., 2018). Future longitudinal

studies are warranted to test whether insight improving interventions decrease suicide risk in psychosis.

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***Conflict of Interest**

The authors declare that there are no conflicts of interest in relation to the subject of this study.

Contributors

JDLM, RD and ASD provided the initial design for the project. JDLM, MDF, OA and BDRW were involved in the recruitment, data collection and data management. JDLM managed the literature searches and wrote the first draft of the manuscript. KM, GAD, PBJ, RAA, MCR, BCF, RMM, PD and CM contributed to the interpretation of the findings and amended the first draft accordingly. All authors contributed to and agreed with the final version of the manuscript.

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Table(s)

Table 1. Demographic and clinical characteristics of the AESOP sample

	Total sample N=181	With previous SA n = 16 (9.9%)	Without previous SA n = 146 (90.1%)	Statistic	p-value
Age at first contact, years	30.5 ± 11.3	31.4 ± 11.5	31.4 ± 11.2	t=-0.0	0.97
Gender, males	101 (55.8)	8 (50.0)	78 (53.4)	X^2=0.1	0.79
Level of education					
No qualifications	51 (31.5)	9 (56.2)	42 (28.8)	X^2=5.0	0.02
≥GCSE	111 (68.5)	7 (43.7)	104 (71.2)		
Unmarried	111 (67.7)	9 (56.2)	99 (67.8)	X^2=0.8	0.35
Living alone	52 (31.0)	5 (39.0)	45 (28.9)	X^2=0.4	0.53
Unemployed	78 (44.6)	8 (50.0)	61 (41.8)		
Ethnicity				X^2=0.2	0.63
White	101 (55.8)	10 (62.5)	82 (56.2)	X^2=1.4	0.23
Black	61 (33.7)	3 (18.7)	49 (33.6)	X^2=1.0	0.30
Other	19 (10.5)	3 (18.7)	15 (10.3)		
DUP: days, median	49.5	51	47	U	0.06
Diagnosis (ICD-10)					
Schizophrenia spectrum	118 (65.2)	10 (62.5)	93 (63.7)	X^2=0.0	0.92
Mania with psychosis	31 (17.1)	0 (0)	30 (20.5)	X^2=4.0	0.04
Psychotic depression	32 (17.7)	6 (37.5)	23 (15.7)	X^2=4.6	0.03
Drugs use	103 (58.9)	7 (46.7)	83 (58.4)	X^2=0.8	0.38
Alcohol use	152 (84.4)	14 (87.5)	124 (85.5)	X^2=0.0	0.83
Insight scores					
Recognition	6.0 ± 3.0	7.6 ± 1.9	5.9 ± 3.0	t=3.1	<0.01
Relabelling	4.7 ± 3.6	5.5 ± 3.3	4.7 ± 3.7	t=0.82	0.41
Compliance	3.2 ± 1.5	4.0 ± 1.4	3.2 ± 1.5	t=1.9	0.05
Total Insight	13.6 ± 6.6	17.2 ± 5.0	13.4 ± 6.7	t=2.1	0.03
Psychopathology					
Positive	4.0	4.5	4.0	U	0.26
Negative	1.0	2.0	0.0	U	0.05
Disorganization	0.0	0.0	0.0	U	0.51
Mania	1.0	0.0	1.0	U	0.07
Depression	0.0	5.0	0.0	U	<0.01
Neurocognition					
Full Premorbid IQ	97.2 ± 14.6	97.6 ± 17.5	98.3 ± 14.2	t=-0.2	0.86
Current IQ	89.6 ± 16.0	89.0 ± 16.0	91.0 ± 16.5	t=-0.4	0.69
TMT-A (seconds)	47.2 ± 27.0	50.0 ± 24.0	45.1 ± 24.8	t=0.6	0.53
TMT-B (seconds)	107.3 ± 62.5	127.2 ± 77.3	102.7 ± 60.3	t=1.2	0.21
TMT-B-A (seconds)	60.9 ± 46.4	77.2 ± 68.9	58.6 ± 45.4	t=0.9	0.40

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses study. SA: suicide attempts. GCSE: General Certificate of Secondary Education. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

Table(s)

Table 2. Demographic and clinical characteristics of the GAP sample

	Total sample N=112	With previous SA n = 22 (19.6%)	Without previous SA n = 90 (80.3%)	Statistic	p-value
Age at first contact, years	29.4 ± 9.2	27.8 ± 5.8	29.8 ± 5.8	t = -1.2	0.21
Gender, males	73 (65.2)	13 (59.0)	60 (66.6)	X^2 = 0.5	0.50
Level of education					
No qualifications	18 (66.4)	4 (18.2)	14 (15.9)	X^2 = 0.1	0.79
GCSE	23 (20.9)	5 (22.7)	18 (20.4)	X^2 = 0.1	0.81
Further	42 (38.2)	7 (31.8)	35 (39.8)	X^2 = 0.5	0.50
University	27 (24.5)	6 (27.3)	21 (23.8)	X^2 = 0.1	0.74
Unmarried	84 (75.7)	16 (72.7)	68 (76.4)	X^2 = 0.1	0.72
Living alone	40 (36.0)	11 (50.0)	29 (32.5)	X^2 = 2.3	0.13
Unemployed	69 (62.7)	10 (45.4)	59 (67.0)	X^2 = 3.5	0.06
Ethnicity					
White	29 (26.1)	9 (40.9)	20 (22.5)	X^2 = 3.1	0.08
Black	49 (44.1)	6 (27.2)	43 (48.3)	X^2 = 3.2	0.07
Other	33 (29.7)	7 (31.8)	26 (29.2)	X^2 = 0.1	0.81
DUP: days, median	42	36	60	U	0.85
Diagnosis (ICD-10)					
Schizophrenia spectrum	86 (77.5)	15 (71.4)	71 (78.9)	X^2 = 0.5	0.46
Mania with psychosis	16 (14.4)	3 (14.3)	13 (14.4)	X^2 = 0.0	0.98
Psychotic depression	9 (8.1)	3 (14.3)	6 (6.6)	X^2 = 1.3	0.25
Cannabis use	81 (72.3)	18 (81.8)	63 (70.0)	X^2 = 1.2	0.27
Alcohol use	68 (75.6)	14 (87.5)	54 (72.9)	X^2 = 1.5	0.22
Insight scores					
Recognition	4.9 ± 3.3	6.2 ± 2.7	4.7 ± 3.3	t = 2.0	p=0.05
Relabelling	4.9 ± 3.4	6.4 ± 3.1	4.5 ± 3.4	t = 2.2	p=0.03
Compliance	3.7 ± 1.8	4.3 ± 1.8	3.6 ± 1.8	t = 1.6	p=0.11
Total Insight	13.6 ± 7.3	16.8 ± 6.4	12.8 ± 7.4	t = 2.2	p=0.03
Psychopathology					
Positive	9.2 ± 4.4	8.7 ± 4.3	9.3 ± 4.4	U	0.47
Negative	11.9 ± 6.1	12.0 ± 5.6	11.9 ± 6.2	U	0.95
Disorganization	6.4 ± 2.7	5.5 ± 2.3	6.6 ± 2.8	U	0.37
Mania	5.4 ± 2.2	4.8 ± 1.1	5.5 ± 2.4	U	0.98
Depression	4.8 ± 4.7	6.0 ± 4.6	4.5 ± 4.8	t = 1.2	0.24
Neurocognition					
Premorbid Full IQ	90.5 ± 10.6	91.9 ± 9.6	90.1 ± 10.8	t = 0.6	0.52
Current IQ	88.4 ± 25.3	93.9 ± 14.1	87.1 ± 27.3	t = 1.0	0.31
TMT-A (seconds)	47.0 ± 20.9	41.6 ± 17.1	48.3 ± 21.7	t = -1.2	0.23
TMT-B (seconds)	119.5 ± 74.0	97.7 ± 56.1	125.2 ± 77.4	t = -1.4	0.16
TMT-B-A (seconds)	71.8 ± 62.4	60.3 ± 49.6	74.8 ± 65.4	t = -0.8	0.38

GAP: Genetics and Psychosis study. SA: suicide attempts. GCSE: General Certificate of Secondary Education. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

Table(s)

Table 3. Univariable analysis: Kaplan-Meier log-rank tests of equality of survival distributions for nominal variables

		AESOP				GAP			
Risk factor		**Events expected**	**Events observed**	**Log-rank test (X^2)**	**p-value**	**Events expected**	**Events observed**	**Log-rank test (X^2)**	**p-value**
Gender	Male	12.8	11	0.75	0.39	11.7	12	0.03	0.86
	Female	11.1	13			6.3	6		
Age at first contact	<28 years	11.7	12	0.00	0.95	**9.8**	**14**	**4.01**	**0.04**
	>28 years	12.3	12			**8.2**	**4**		
Education level	No qualifications	2.8	2	0.22	0.64	2.8	4	1.58	0.66
	GCSE or higher	6.2	7			14.2	13		
Marital status	Unmarried	6.0	5	0.67	0.41	12.9	14	0.49	0.48
	Married	2.3	4			4.1	3		
Living status	Alone	7.6	10	1.25	0.26	**6.1**	**11**	**4.46**	**<0.01**
	Not alone	16.4	14			**10.9**	**6**		
Employment status	Unemployed	10.4	8	1.01	0.32	10.7	9	1.01	0.32
	Employed	13.6	16			6.3	8		
Ethnicity	White	13.4	16	1.84	0.40	4.4	7	2.34	0.31
	Black	7.9	5			7.5	6		
	Other	2.6	3			5.0	4		
Previous SA	Absent	21.6	16	23.11	<0.01	14.5	10	10.06	<0.01
	Present	2.4	8			3.5	8		
DUP	Short	12.0 (<49d)	11	0.22	0.64	8.6 (<42d)	10	0.72	0.40
	Long	12.0 (>49d)	13			8.4 (>42d)	7		
Diagnosis	Schizophrenia	15.2	16	0.76	0.68	13.9	17	3.24	0.19
	Mania	4.5	3			2.5	1		
	Depression	4.3	5			1.4	0		
Drugs use	Absent	10.4	9	0.38	0.54	4.9	3	0.98	0.32
	Present	13.6	15			13.0	15		
Alcohol use	Absent	3.6	0	4.49	0.03	3.2	2	0.97	0.32
	Present	20.4	24			9.8	13		

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses study. GAP: Genetics and psychosis study. SA: suicide attempts. GCSE: General Certificate of Secondary Education.

DUP: Duration of untreated psychosis. d: days

Table(s)

Table 4. Univariable Cox regression analyses for continuous variables

	AESOP			GAP		
Risk factor	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Neurocognition						
Full premorbid IQ	1.02	0.99 - 1.06	0.21	0.95	0.91 - 1.00	0.09
TMT-B-A	1.01	1.00 – 1.02	0.01	0.83	0.99 – 1.01	0.83
Psychopathology						
Positive	1.08	0.93 – 1.24	0.33	1.02	0.91 – 1.15	0.70
Negative	0.93	0.74 – 1.17	0.53	1.06	0.99 – 1.14	0.10
Disorganization	0.84	0.51 – 1.38	0.48	0.98	0.82 – 1.17	0.83
Mania	0.96	0.80 – 1.16	0.68	0.83	0.59 – 1.16	0.20
Depression	1.57	1.30 – 1.89	<0.01	1.09	0.99 – 1.18	0.08
Insight						
Recognition	1.14	0.98 – 1.34	0.09	1.09	0.94 – 1.26	0.24
Relabeling	1.06	0.96 - 1.18	0.25	1.10	0.95 - 1.26	0.19
Compliance	1.30	0.99 – 1.71	0.06	1.36	1.01 – 1.83	0.04
Total insight	1.06	0.99 – 1.13	0.08	1.06	0.99 – 1.14	0.08

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses study. GAP: Genetics and Psychosis study.

SA: suicide attempts. DUP: Duration of untreated psychosis. IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

Table(s)

Table 5. Multivariable Cox Regression models in the AESOP and GAP cohorts

AESOP					GAP				
Risk factor		**HR**	**95% CI**	**p-value**	**Risk factor**		**HR**	**95% CI**	**p-value**
Previous SA	Present	2.75	0.90 – 8.52	0.07	Age at first contact	<28 years	5.31	0.82 – 34.16	0.08
	Absent	1.00				>28 years	1.00		
TMT B-A		1.00	0.99 – 1.01	0.13	Living status	Alone	4.56	0.98 – 21.12	0.05
Depression		1.55	1.22 – 1.97	<0.01		Not alone	1.00		
Recognition		1.02	0.69 – 1.50	0.92	Previous SA	Present	5.17	1.32 – 20.29	0.02
Compliance		1.08	0.70 – 1.67	0.73		Absent	1.00		
Total insight		1.04	0.87 – 1.24	0.65	Full Premorbid IQ		0.95	0.87 – 1.03	0.24
					Depression		1.16	1.00 – 1.35	0.04
					Compliance		1.41	0.83 – 2.38	0.20
					Total Insight		1.06	0.90 – 1.24	0.50

AESOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses study. GAP: Genetics and Psychosis study. SA: suicide attempts.

IQ: Intelligence Quotient. TMT: Trail Making Test (Reitan, 1958)

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