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Tobacco smoking and nicotine dependence in first episode and established psychosis

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Abstract

Aim

People with psychotic disorders have increased premature mortality in comparison with the general population, with high rates of cigarette use a contributing factor. We aimed to describe the prevalence of cigarette use and nicotine dependence (ND) in first episode psychosis (FEP), and established psychosis; and to investigate associations between clinical symptoms and ND.

Methodology

Smoking and clinical data were collected from two cohorts: 181 people with FEP recruited as part of the Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study and from 432 people with established psychosis recruited as part of the Improving physical health and reducing substance use in psychosis randomised controlled trial (IMPACT RCT).

Results

The prevalence of cigarette smoking was 78% in FEP and 62% in established psychosis. Forty nine percent (n=60) of smokers in the FEP cohort and 69% (n=183) of smokers with established psychosis were highly nicotine dependent. Being a highly nicotine dependent smoker was significantly associated with higher PANSS positive symptom scores ($F= 5.480$ $p= 0.004$), and with decreased scores on the Rosenberg self-esteem scale ($F=3.261$, $p=0.039$) in established psychosis. There was no diagnostic specificity identified in relation to smoking or ND in both groups.

Conclusion

High rates of cigarette usage and nicotine dependence are problems from the early stages of psychosis. ND is higher in people with established psychosis. Smoking cessation strategies as part of comprehensive management of psychotic disorders at every stage require further development and evaluation.

Keywords: schizophrenia; psychotic; smoking; substance use; addiction; physical health

1.0 Introduction

1.1 Smoking carries an increased physical health burden in people with mental illnesses, and people with a diagnosis of a mental disorder account for an estimated 40% of all cigarette consumption (Substance Abuse and Mental Health Services Administration 2013, Meltzer H et al., 1996, Office for National Statistics 2017). People with a diagnosis of schizophrenia have smoking rates 6-fold higher than the general population (de Leon and Diaz 2005). The most consistent estimate of smoking prevalence in schizophrenia in the UK is a rate of 60-65% (Smith et al., 2007, Krishnadas et al., 2012, Kelly and McCreadie 1999, Gardner-Sood et al., 2015), a figure reflected in international studies (Dickerson et al., 2013b, Margolese et al., 2004, Morgan et al., 2013, de Leon et al., 1995, Dickerson et al., 2018b). This is despite the significant reduction of smoking observed in the general population over the past 30 years (39% in 1980 and 17% in 2015) (Office for National Statistics 2017). Those with psychotic disorders also smoke more heavily compared to the general population (Lohr and Flynn 1992, Kelly and McCreadie 1999, Ziedonis and George 1997, Hughes et al., 1986). While 11% of smokers in the general population are heavy smokers, 60% (Kelly and McCreadie 1999) -80% (Hughes 1986) of those with schizophrenia and other psychotic disorders smoke 25 or more cigarettes daily.

1.2 Nicotine dependence (ND) in schizophrenia

Nicotine dependence (ND) has been less frequently measured in people with psychotic disorders. ND reflects not only the frequency and quantity of smoking, but features such as tolerance and withdrawal, such as the time to first cigarette use per day (Heatherton et al., 1991). It is associated with increased difficulty in smoking cessation. Prevalence rates for high ND in schizophrenia of 32% (Aguilar et al., 2005) to 38% in a UK study (Krishnadas 2012) have been reported, with overall rates of ND ranging from 38% (Yee et al., 2015) to 76% (Patkar et al., 2002). The high prevalence of cigarette use and ND in those with psychotic disorders renders them especially vulnerable to adverse physical health consequences (Morris et al., 2006, McClave et al., 2010, de Leon and Diaz 2005, Dickerson 2013b).

1.3 Smoking and clinical symptoms

Conflicting associations have been described between cigarette smoking and psychotic symptoms in schizophrenia. Cross sectional studies in established psychosis have reported associations between tobacco use and reduced negative (Zhang et al., 2012, Zhang et al., 2007, Smith et al., 2001), and positive symptoms (Zhang 2007). However, findings are inconsistent, with some studies finding no association between smoking status and clinical

symptoms (Barnes et al., 2006, Kelly and McCreadie 1999, Herran et al., 2000, Kotov et al., 2010), and others linking current smoking with a greater severity of positive (Goff et al., 1992, Corvin et al., 2001, Zhang et al., 2013) and negative symptoms (Goff 1992, Cooper et al., 2012, Iasevoli et al., 2013, Tidey and Williams 2007) and worse cognitive function and functional outcomes (Depp et al., 2015).

The majority of studies relate to established psychosis, with just three studies examining links between clinical symptoms and smoking in first episode psychosis (FEP) (Grossman et al., 2017, Zhang 2013, Misiak et al., 2015). In a cross sectional study of 109 FEP patients, cigarette smoking was associated with fewer depressive and negative symptoms (Misiak 2015), while in a Chinese study of 244 first episode schizophrenia (FES) smoking was associated with increased total and positive psychotic symptoms (Zhang 2013). A more recent cross sectional study of 140 FEP patients found no relationship between cigarette smoking and psychotic or depressive symptoms (Grossman 2017).

1.4 Nicotine dependence and clinical symptoms in established psychosis and FEP

Fewer studies have assessed the association between nicotine dependence and psychotic symptom severity in people with psychosis. Some cross sectional studies identified positive associations between ND and total and positive psychotic symptoms, (Krishnadas 2012, Aguilar 2005), with others reporting associations with decreased negative but not positive symptoms (Yee 2015, Patkar 2002, Douglas M. Ziedonis et al., 1994). Nicotine dependence was associated with worse scores on the Clinical Global Impression scale (Herran 2000) and worse functional outcomes (Depp 2015). The single study in FEP found reduced depressive and negative symptoms in those with severe ND compared to non-smokers (Misiak 2015).

The paucity of available research and the equivocal study findings preclude definitive interpretations of the relationship between cigarette smoking, nicotine dependence and clinical symptoms in psychosis.

1.5 Study aims:

To assess the role of smoking in psychotic disorders we aimed to:

- A) Describe the characteristics and prevalence of cigarette use in FEP and established psychosis cohorts.
- B) Determine the rates of nicotine dependence in both cohorts, and examine for associations between nicotine dependence and demographic and clinical characteristics.

2. Material and Methods

2.1 Cohorts and settings

First episode psychosis (FEP) cohort

Baseline data from 181 FEP patients recruited in both inpatient and outpatient settings in three UK Mental Health Trusts as part of the Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study, part of the NIHR-funded, Improving Health and Reducing Substance Use in Psychosis (IMPACT) programme ((Lally et al., 2018a, Lally et al., 2017) Gaughran et al, submitted).

Established psychosis cohort

Baseline data from 432 patients with established (multi-episode) psychosis recruited from community mental health teams (CMHTs) in five Mental Health NHS Trusts as part of the NIHR funded IMPACT randomised controlled trial (RCT) (Improving physical health and reducing substance use in severe mental illness) (Gaughran et al., 2013, Gaughran et al., 2017).

2.2 Subjects

FEP cohort

Participants were aged 18-65 years and were proficient in English with no requirement for an interpreter. Patients were eligible if they met the ICD-10 criteria for psychosis (ICD-10 codes F20-29 and F30-33) diagnosed utilising the OPCRIT (McGuffin et al., 1991) and had made first contact with health services for psychotic symptoms not more than 12 months previously. Patients were consented as soon after first presentation with psychosis as possible. Exclusion criteria included comorbid major medical illness or neurological disease; diagnosed severe learning disability; an organic cause for their psychosis; or history of previous contact with health (GP or Psychiatric) services for the presence of psychosis.

Established psychosis cohort

The inclusion criteria were as follows: capacity to provide written informed consent to participate (Lally et al., 2018b); aged between 18-65 years old; a primary diagnosis of a psychotic illness (ICD-10 diagnosis: F20-29, including schizophrenia, schizoaffective disorder, bipolar affective disorder and delusional disorder, F31.2, F32.3 and F33.3), Exclusion criteria included a primary diagnosis of intellectual disability (as defined by ICD-10 codes F70-F79 for intellectual disabilities); a first episode of psychosis (FEP); a primary

substance misuse disorder (excluding tobacco); a serious physical illness that could independently impact metabolic measures; pregnant or up to six months postpartum; and receiving intensive input for a medical or terminal condition.

2.3 Clinical and sociodemographic variables

Sociodemographic and clinical data were collected including gender, age, ethnicity, education, relationship status and living circumstances and diagnosis along with self-reported duration of illness (established psychosis cohort only).

Participants' mental health status was measured using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1989); depression was assessed using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery 1979) in the established psychosis cohort and Calgary Depression Rating Scale (CDRS) (Addington et al., 1990) in those with FEP. Alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT) (Saunders 1993). In addition, the Rosenberg Self Esteem scale was applied in the established psychosis cohort (Rosenberg 1965).

2.4 Tobacco Smoking

Current smoking use was recorded using the Fagerström Tolerance Questionnaire (FTQ) (Fagerstrom and Schneider 1989, Fagerstrom 1978, Heatherton 1991). The FTQ measures nicotine dependence. It is an 6 item scale which produces a range of scores from 0-11.

Data for all measures were collected through face-to-face interviews conducted by trained research assistants. Total scores on the FTQ were derived from individual scale items.

Smoking status was assessed at baseline using the question 'do you currently smoke (at least one per week)?' All participants who smoked were administered the FTQ to measure nicotine dependence. ND has been classified as very high nicotine dependence (score of >7), medium to high nicotine dependence (score of 5-7), mild nicotine dependence (score 2-4) and low or absent dependence (score 1-2)(Horn et al., 2003, Kimberly et al., 1999).

Based on the exploratory nature of our study, and the sample size, dichotomized FTQ scores were used. For this study we categorized the FTQ scores into two categories, high and low dependence based on a median split in the FTQ total score(Morris et al., 2016). On the basis of the FTQ scores, smokers in both the FEP and the established psychosis cohorts were classified as displaying high dependence (FTQ ≥ 5 (equivalent to moderate to very high

dependence); or low dependence ($FTQ \leq 4$ (equivalent to mild to low dependence)); non-smokers were the third category.

We recorded the total number of all types of cigarettes and other forms of tobacco-smoked daily. We classified those who smoked ≥ 20 cigarettes or other tobacco products to be heavy smokers, as used in other studies (Kay-Lambkin et al., 2013, Alati et al., 2004, Grossman 2017).

2.5 Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp). Descriptive measures were used for the basic demographic and clinical variables as well as for variables relating to the evaluation of smoking frequency and severity of nicotine dependence. Cross-comparisons were performed to calculate smoking prevalence by gender, ethnicity, diagnostic group and nicotine dependence status. The student-t test for parametric data and the Chi square (χ^2) test for categorical variables were employed. Comparisons between groups for continuous variables were conducted using independent *t*-tests and Analysis of Variance (ANOVA). Demographic and clinical variables for high dependence smokers, mild dependence smokers and non-smokers were compared using an ANOVA. Post hoc analyses using the Tukey HSD post hoc criterion for significance were conducted where ANOVA demonstrated significant differences between the group means. All statistical tests were two-sided and a *p* value ≤ 0.05 was considered statistically significant.

3. Results

3.1 The demographic and clinical characteristics of those in the total FEP and established psychosis study populations are shown in supplementary tables 1 and 2.

Seventy eight percent of those with FEP and 62% of those with established psychosis were current smokers (Table 1). Those with FEP smoked a mean of 10.7 (SD=6.6) (median=10.0) cigarettes per day, while in those with established psychosis the mean number of cigarettes smoked per day was 16.4 (SD=8.5) (median=16.0). Eighteen percent (*n*=43) of those with established psychosis smoked more than 20 cigarettes per day, compared to 3% (*n*=2) of those with FEP.

The mean FTQ score in those with established psychosis was 5.2 (SD=1.6) (median=5.0) and 4.5 (1.9) (median=5.0) in those with FEP. The rate of high ND was 69% in established psychosis, and 49% in FEP.

3.2 First episode psychosis

There were 141 current smokers (81% of males (n=100) and 71% of females (n=41). Females smoked on average 12.0 (SD=8.3) cigarettes per day and males 10.3 (SD=5.8) ($t=1.023$, $p=0.310$).

A higher proportion of people with a diagnosis of a non-schizophrenia FEP (85%; n=51) smoked compared to those with a diagnosis of first episode schizophrenia (71%; n=50) ($\chi^2=3.433$, $p=0.049$). Only two cases (both female) were heavy smokers, smoking more than 20 cigarettes per day.

The criteria for ND were met by 74% (n=120), with 49% (n=60) having high dependence with no gender differences noted. There were no significant differences between those of different ethnicities in severity of ND or number of cigarettes smoked per day. Nor were any significant differences detected in diagnostic subgroups, psychotic symptoms or depressive symptoms between ND categories and non-smokers (Table 2).

Those with high ND had significantly higher mean AUDIT scale scores (mean 13.6 (SD=11.0), compared to those with low dependence (mean=9.2 (SD=7.2) and non-smokers (mean=7.7 (SD=7.8) ($F=5.968$, $p=0.03$).

3.4 Established psychosis

Among 432 patients, 268 (62%) were current smokers and 61% (n=264) met criteria for ND. Of those, 83 (31%) met criteria for low nicotine dependence, and 183 (69%) for high nicotine dependence.

Males (73%, n=178) were more likely than females (48%, n=90) to smoke ($\chi^2=27.085$, $p<0.001$) (supplementary table 2), although the average number of cigarettes smoked daily was similar in males (16.3 (SD=8.6)) and females (16.8 (SD=8.4) ($t=0.431$, $p=0.667$).

A similar proportion of male (16.1%; n=26) and female smokers (20.5%, n=17) were heavy smokers ($\chi^2=0.708$, $p=0.251$). Those of white ethnicity were more likely to be heavy smokers (23.3%; n=31) than those of other ethnic groups ($\chi^2=8.092$, $p=0.044$). A trend was evident towards a smaller proportion of people with a diagnosis of schizophrenia being heavy smokers (14.0%; n=24) compared to those with a diagnosis of affective psychosis (24.6%; n=16) ($t=3.474$, $p=0.053$).

Increased rates of high ND were observed in males (52%; n=127) compared to females (30%; n=56) ($\chi^2=27.5$; $p<0.001$); in those of white ethnicity (49%; n=108) compared to those of black ethnicity (37%; n=50), Asian ethnicity (20%; n=3), and those of mixed or other ethnicity (31%; n=9) ($\chi^2=17.068$, $p=0.009$); and in people living in supervised accommodation

(52.7%; n=49) compared to those living in other settings ($F=30.036$, $p<0.001$) (supplementary table 2).

On tests of between-participants effects, dependence status was significantly associated with PANSS positive symptom scores ($F= 5.480$ $p= 0.004$) and trended towards a significant association with total PANSS scores ($F=2.914$, $p=0.055$), but not PANSS negative symptoms scores ($F = 0.397$; $P = 0.672$)(Table 3).

Those with high ND had greater rates of depression (defined by MADRS score > 6) (46%; n=121) compared to those with low ND (16%; n=42) and non-smokers (38%; n=98) ($x=6.397$; $p=0.041$), although there was no difference on continuous MADRS measures.

Those with high ND had lower scores on the Rosenberg self-esteem scale (mean=17.1 (SD=5.6), compared to those with low dependence (mean=19.0 (SD=6.6)) ($F=3.261$, $p=0.039$). Those with high ND had lower scores than non-smokers (mean=18.3 (SD=5.3), but this did not meet statistical significance ($p=0.171$).

Patients with high nicotine dependence had higher mean AUDIT scores (mean 7.2 (SD=6.1), compared to those with low dependence (mean=6.2 (SD=5.2) and non-smokers (mean=3.4 (SD=3.6) ($F=12.616$, $p<0.001$).

4.0 Discussion

Smoking rates are high in both FEP (78%) and established psychosis (62%) despite the reductions in cigarette use in the general population. Our 78% figure in FEP population is higher than previous FEP studies that identified rates of 36-53% (Misiak 2015, Zhang 2013, Grossman 2017) and over 3 times higher than rates in the UK general population for a comparable age range (16-34 years)(Office for National Statistics 2017). Similar rates of cigarette use (78%) were identified in an Australian cohort of 126 FEP patients(Wade et al., 2005).

High levels of ND were seen in both FEP and established psychosis, but high ND was more prevalent in established psychosis. This suggests that cigarette use is established early in the course of psychotic illness, if not before (Gurillo et al., 2015), while dependence increases over time. An association between duration of illness and ND status has not been previously identified (Krishnadas 2012). However, it remains possible that difference in ND levels between stages of illness may be explained by secular trends. The variance in degree of ND may relate to longitudinal changes in social and legal policy in relation to cigarette use such as smoking being prohibited in public places, and higher costs, potentially making it easier to refrain from smoking in public places and the cost of cigarettes limiting the number

smoked in the younger FEP cohort.

4.1 Nicotine dependence in Established psychosis

Age, relationship status, level of education and duration of illness did not differ between smokers and non-smokers, or with degree of ND. In those with established psychosis, males were more likely to smoke and have greater nicotine dependence than females, in keeping with previous work (de Leon and Diaz 2005, Dixon et al., 2007), although this was not evident in those with FEP. People with established psychosis of white ethnicity were more nicotine dependent and more likely to smoke more than 20 cigarettes per day in comparison to those from other ethnic groups, in keeping with previous work (Dixon 2007) and mirroring general population studies (Trinidad et al., 2009, Caraballo et al., 1998, Hahn et al., 1990).

The higher rate of ND in those living in supported accommodation was notable and may offer opportunity for intervention. People who need supervised accommodation often have functional impairment secondary to their psychotic disorder and the greater ND in this population may make smoking cessation more challenging.

4.2 Diagnostic subgroups and tobacco smoking

We found no relationship between ND and diagnosis. Prior studies have found a lack of diagnostic specificity with smoking status in both FEP (Grossman 2017), (Kotov 2010) and established psychosis (Corvin 2001), but have not examined ND.

We noted higher rates of smoking in non-schizophrenia FEP compared to first episode schizophrenia (FES). Only two cases (1%) in the FEP group were heavy smokers, much less than 19% (27/140) identified in a recent cross sectional analysis of smoking in FEP (Grossman 2017).

The mean number of cigarettes smoked per day in the established psychosis group of 16.4, is higher than the general population average of 11 cigarettes per day (Office for National Statistics 2013), although there was no impact of diagnosis of schizophrenia versus non-schizophrenia psychotic disorders.

4.3 Clinical correlates

In established psychosis, being a highly nicotine dependent smoker was associated with increased positive symptoms. This replicates two prior studies, which identified a similar relationship in schizophrenia (Krishnadas 2012, Aguilar 2005), and expands on these findings with the inclusion of schizophrenia and other psychotic disorders. A recent

prospective cohort study identified associations between smoking and increased positive, negative and depressive symptoms in 1094 people with non affective psychosis who smoked, indicating that smoking is associated with worsening of clinical state(Vermeulen et al., 2019).

For the first time, we identified a significant relationship between high ND and lower self-esteem in people with established psychosis. This is a novel finding and one, which may point towards strategies to address low self-esteem in aiding smoking reduction and cessation in this population. In the general population, most evidence exists in adolescent and young adult populations to support associations between improved self-esteem and lower smoking rates(Carvajal et al., 2000). This relationship seems to be more evident in males, with increased smoking behaviour and pro-smoking beliefs relating to low self esteem(Hale et al., 2015).

To the best of our knowledge this is the second study to investigate associations between ND and clinical symptoms in early psychosis. In contrast to the previous study in FES which identified an association between lower negative and depressive symptoms in those with severe ND compared to non-smokers(Misiak 2015), we found no significant associations between clinical symptoms and ND compared to non-smokers.

Other studies in FES identified associations between smoking and positive symptoms (Zhang 2013), though similar to Grossman et al, we did not identify associations between smoking and clinical symptoms in our FEP group(Grossman 2017).

As expected, smokers with high ND in both populations had higher rates of hazardous drinking than non-smokers. Previous epidemiological studies have indicated increased rates of alcohol use disorders in smokers with established psychosis (Degenhardt and Hall 2001, Hartz et al., 2014).

4.4 Strengths and Limitations

The cross-sectional nature of this study limits interpretation regarding casual inference regarding the relationship between ND, and cigarette smoking and clinical symptoms. However, our established psychosis population were a reasonably stable cohort living in the community with average illness duration of 15 years. The use of multiple statistical tests may have increased the risk of type I errors, and our findings require replication in longitudinal cohorts.

The use of cigarettes was self-reported, thus raising the possibility of reporting bias in that patients may have inaccurately reported consumption. However, we also recorded ND as measured by the FTQ, with the measure of ND not wholly reliant on establishing heavy smoking, the frequency of cigarette use, or duration of smoking (which might be affected by self-report measures of cigarette use). The use of a validated scale to measure ND provides a reliable measure of smoking use in this population. Further, our findings in relation to ND rates are largely consistent with prior work in psychotic disorders. We did not include data on antipsychotic medication or use of illicit substances, which may potentially have influenced outcomes. Specifically in our established psychosis cohort, some of whom were treated with clozapine, smoking may have been associated with induction of antipsychotic metabolism, leading to reductions in plasma antipsychotic concentrations, and potentially impairing antipsychotic effectiveness (Lally et al., 2016). Though in those with maintenance medication regimens, antipsychotic dosing may have been adjusted to account for this to maintain clinical stability. However, this remains speculative, as medication use and doses are not measured in this study.

4.5 Need for smoking cessation implementation

Despite these limitations, our study indicates that smoking is highly prevalent across the lifespan of psychotic illness, and increased focus on smoking cessation in these populations is required given the reduced life expectancy and burden of (Azad et al., 2016) disease in these populations (Correll et al., 2017, Hjorthøj et al., 2017). Cigarette smoking in psychotic disorders further exacerbates the risk of cardiovascular disease, respiratory disease and premature mortality (Bobes et al., 2010, Correll 2017, Kelly et al., 2011), doubling the risk of natural cause mortality (Dickerson et al., 2018a). An 11 year follow up of 517 people with schizophrenia showed an overall Standardised Mortality Ratio of 2.80, with smoking found to be strong predictor of death with a relative risk of 4.66 (Dickerson et al., 2013a). Further, a prospective study showed that smoking was associated with increased psychotic symptoms, refuting that this is due to reverse causation by mechanisms such as self-medication to improve psychotic symptoms (Vermeulen 2019). The potential for smoking as a risk factor for the development of schizophrenia has been shown, with those who smoke more than 10 cigarettes a day at the age of 16, having a three fold increased risk of developing a psychotic disorder by the age of 30 (Mustonen et al., 2018), adding to findings from meta analysis indicating that cigarette smoking is associated with the earlier onset and increased risk of psychotic illness (Gurillo 2015). Until recently, clinicians have been unduly pessimistic about the prospect of reducing smoking rates in psychosis. However, study

findings have demonstrated that people with schizophrenia want to stop smoking and that it is possible to help them to do so (Banham and Gilbody 2010, Hall and Prochaska 2009, Ziedonis et al., 2008, Gandhi et al., 2019). Abstaining from cigarette use in schizophrenia does not worsen mental state (Evins et al., 2007), and the use of smoking cessation agents such as bupropion and varenicline can be successfully used without worsening psychosis (Tsoi et al., 2013).

It appears that levels of ND are broadly consistent across diagnostic groups, as are factors contributing to increased smoking and higher levels of ND. Potentially important contributing factors (and avenues for therapeutic intervention) in established psychosis include being housed in supervised accommodation, and lower self-esteem in smokers with higher ND.

6. Conclusion

We found a significant association between ND and positive symptoms of psychosis in established psychosis, though no such relationship was identified in FEP. Our study builds on prior research in established psychosis to indicate that smoking and ND remain significant health risks in this population. Larger prospective studies, to explore relationships between smoking, ND and clinical symptoms are required. The 3-fold greater smoking rates than the general population highlights the need for a reinvigorated approach to smoking.

Contributors.

Authors JL and FG designed the study. Author JL undertook the statistical analysis, and author JL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

MDF has received honoraria for lectures from Janssen and Sunovion

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All other authors (JL, GS, PGS, ZA, KG, KI, KCM, SS, AM) declare they have no conflict of interest.

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