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Anoop Sankaranarayanan, Vanessa Clark, Amanda Baker, Kerrin Palazzi, Terry J. Lewin, Robyn Richmond, Frances J. Kay-Lambkin, Sacha Fila, David Castle, Jill M. Williams



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Reducing smoking reduces suicidality among individuals with psychosis:  
Complementary outcomes from a Healthy Lifestyles intervention study<sup>☆</sup>

Anoop Sankaranarayanan<sup>a, b, \*, 1</sup>, Vanessa Clark<sup>b</sup>, Amanda Baker<sup>b</sup>, Kerrin Palazzi<sup>c</sup>,  
Terry J Lewin<sup>a, b, d</sup>, Robyn Richmond<sup>e</sup>, Frances J Kay-Lambkin<sup>d, f</sup>, Sacha Filia<sup>g, h</sup>,  
David Castle<sup>i, j, k</sup>, Jill M Williams<sup>l</sup>

<sup>a</sup>Hunter New England Mental Health Service

<sup>b</sup>School of Medicine and Public Health, University of Newcastle, Callaghan,  
NSW, Australia

<sup>c</sup>Public Health Program, Hunter Medical Research Institute (HMRI), Newcastle,  
NSW, Australia

<sup>d</sup>Centre for Translational Neuroscience and Mental Health, University of  
Newcastle

<sup>e</sup>School of Public Health and Community Medicine, University of New South  
Wales, Sydney, Australia

<sup>f</sup>NHMRC Centre for Research Excellence in Mental Health and Substance Use,  
National Drug and Alcohol Research Centre, University of New South Wales

<sup>g</sup>Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash  
University, Victoria, Australia

<sup>h</sup>Alfred Hospital, 55 Commercial Road, Prahran, Melbourne, Victoria, Australia

<sup>i</sup>St. Vincent's Hospital, PO Box 2900, Fitzroy, Victoria, Australia

<sup>j</sup>The University of Melbourne, Parkville, Melbourne, Victoria, Australia

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<sup>☆</sup> Registration details are as follows: Registry: Australian and New Zealand Clinical Trials  
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<sup>1</sup> Present Address: Dr Anoop Sankaranarayanan, Psychiatrist, Community Health Center, 65  
Brunswick Street, Fredericton, NB E3B 1G5

<sup>k</sup>Faculty of Health Sciences, Australian Catholic University, 1100 Nudgee Road, Banyo, Queensland, Australia

<sup>l</sup>Division of Addiction Psychiatry, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

\*Corresponding Author: Telephone: +61 49392900; Fax: +61 49392901.+. E-mail: anoopshank2000@gmail.com

## ABSTRACT

This study sought to explore the impact of smoking reduction on suicidality (suicide ideation and behavior) among people with a psychotic disorder (n=235) who participated in a randomized trial of a healthy lifestyle intervention trial. Suicidality, measured by item -4 of the Brief Psychiatric Rating Scale (BPRS) was the main variable of interest. Measures were collected by research assistants blind to treatment allocation at baseline, at 15 weeks (mid-intervention) and 12 months after baseline. Mediation analysis, adjusted for confounders, was used to determine the relationship between smoking reduction and suicidality and to explore whether this was mediated through depression. At 12 months, smoking reduction was found to be significantly associated with suicidality change; an association was also seen between smoking reduction and depression and depression and suicidality. After adjusting for depression, the association between smoking reduction and suicidality was reduced attenuated but remained statistically significant; the proportion of the total effect that was mediated through depression was 30%. There was no significant association between suicidality and treatment group (vs. controls) over time. Our study

suggests that smoking interventions may have benefits over and above those for improved physical health, by reducing suicidal ideation in people with psychosis.

## **Keywords**

Suicide, suicidality, suicide risk, smoking, schizophrenia, psychosis The Trial

## **Text**

### **1. Introduction**

People living with a severe mental illness (SMI) are at increased risk for substance misuse and suicidal behaviours, the risk being particularly high in those with schizophrenia and major depression (Cooper et al, 2012; Ostacher et al, 2006; Wilhelm et al, 2003). For example, Hartz et al (2014) compared substance use in a multi-ethnic cohort of patients with SMI to that of population based controls and found that individuals with psychotic disorders were more likely to smoke (Odds Ratio, OR 4.6; 95% CI, 4.3-4.9), use alcohol (OR 4.0; 95% CI 3/6-4.4), cannabis (OR 3.5; 95% CI 3.2-3.7) and recreational drugs (OR 4.6; 95% CI 4.3-5.0). High rates of substance use were also described among participants of the Australian Survey of High Impact Psychoses (SHIP) study. Also, more than half the sample had a diagnosis of alcohol abuse / dependence and cannabis abuse / dependence and nearly one-third had evidence of other illicit drug abuse or dependence (Moore et al, 2012). Earlier research promoted the “self-medication hypothesis” to explain the high rates of smoking seen in people with schizophrenia (Lohr & Flynn, 1992; Kumari and Postma, 2005). However, this is not straightforward. For example, while some researchers argue

that smoking is associated with lower incidence of negative symptoms (Smith et al, 2002; Zhang et al, 2012), a recent meta-analysis suggests that daily tobacco use is associated with greater risk of psychosis (Gurillo et al, 2015).

Historically, it has generally been accepted that between 20% and 40% of patients with schizophrenia attempt suicide (Roy, 1986) and 10-15% die by suicide (Drake et al, 1985). More recent work suggests an estimated lifetime suicide prevalence of 4.9% (Palmer et al, 2005) in people with schizophrenia, with suicide deaths usually occurring soon after illness onset. Identified risk factors for suicide and deliberate self-harm (DSH, including suicide attempt) in schizophrenia, include previous depressive disorders, previous suicide attempts, drug misuse, poor adherence to treatment, recent life events (Haw and Hawton, 2005; Hawton et al, 2005; Hor and Taylor, 2010), early life adversities, pain syndromes (Fuller-Thomson and Hollister, 2016) and smoking (Sankaranarayanan et al, 2015).

There is evidence to suggest that smoking cessation reduces suicidal risk; for example, the association between smoking and suicidal behaviours has been shown to be higher among current and ex-smokers compared to never smokers (Li et al, 2012). A recent data-linkage analysis indicates that tight legislation and policies to restrict smoking are associated with a reduction in suicidality in the general population (Grucza et al, 2014). Such studies cannot, however, control for potential confounders that might also influence smoking over an extended time period. Thus, it is conceivable that interventions to address smoking could

potentially also serve to reduce suicidality. Capron et al (2014) investigated the effects of successful and unsuccessful smoking interventions on psychopathology scores (measures of depression and anxiety) in non-psychotic individuals. They found no worsening in psychopathology in those who quit smoking. We are not aware of any previous studies that have specifically studied the impact of smoking cessation on suicidality scores among smokers with SMI. The sub-study reported here aimed to address this gap, by determining the impact of a smoking cessation intervention on suicidality scores among people with a SMI. We hypothesised *a priori* that reduced smoking would be associated with lower suicidality.

## 2. Methods

The current project is a sub-study of a Healthy Lifestyles intervention trial for smokers with SMI, which has been reported in detail elsewhere (Baker et al, 2011; Baker et al, 2015).

While the current analyses and findings complement those of the main study, they have a different purpose. The specific objectives of this sub-study were to:

1. Measure change in suicidality between baseline and 12 months;
2. Examine the association between suicidality and treatment group over time; and

3. Examine the effect reduced smoking had on suicidality, including the potential mediating pathway through depression.

## **2.1. Participants and Procedure**

Smokers with a psychotic disorder (N= 235) were recruited across three sites (in Newcastle, Sydney and Melbourne, Australia). Ethics approval was obtained from Hunter New England Human Ethics Committee (for the lead site) and from each of the other site's university and hospital ethics committees. Participants were included if they were: aged at least 18 years; smoking at least 15 cigarettes per day; diagnosed with a schizophrenia spectrum or bipolar disorder, as confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al, 1998); and taking antipsychotic medication as prescribed for a period of at least two months, with intention to continue for the duration of the study. Exclusion criteria were: not fluent in English; had an organic brain disease, or any medical conditions that would preclude nicotine replacement therapy (NRT). Following a baseline assessment, participants completed a standardised 90-minute face-to-face intervention session, at the conclusion of which they were randomised to a face-to-face intervention addressing smoking, diet and exercise or to a less intensive predominantly telephone-based intervention (comparison condition); both groups were offered NRT (see Baker et al, (2011; 2015) for full study details). All study measures were undertaken by research assistants blinded to treatment allocation at baseline, 15 weeks (mid-intervention) and 12 months after baseline.



## **2.2 Measures**

Smoking (cigarettes/day), depression and suicidality were measured at three time points (baseline, 15 weeks and 12 months post baseline). For the current analyses, these time points were expressed as months (0, 3.5 and 12) and used as a continuous time measure.

### **2.2.1. Suicidality**

We defined suicidality as any active suicidal thoughts or plans or intent or attempt. Suicidality was measured at baseline and follow-up using clinician-rated item 4 of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al, 1993). The BPRS item 4 requires participants to report suicidal thoughts over the previous two week period.

### **2.2.2. Psychiatric symptomatology and quality of life**

Diagnoses were determined using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al, 1998). General functioning was measured using the Global Assessment of Functioning Scale (GAF) (APA, 1994) and 12-item Short Form survey (SF-12) (Ware et al, 1996), which produces Mental Component Scores (MCS) and Physical Health Component Scores (PCS), with lower scores indicating greater disability. The total score for the Beck Depression Inventory (BDI-II) was used to measure current depressive symptoms; the higher the scores, the more severe the depression.

### **2.2.3. Medication Use**

Medication use was self-reported and recorded as psychotropic or general medication.

### **2.2.4. Substance Use**

Tobacco, alcohol and cannabis usage was measured using the Drug Use Scale of the Opiate Treatment Index (OTI) (Darke et al, 1991). The OTI (tobacco; cannabis; alcohol items) provides a measure of average use occasions per day in the month preceding assessment: for example, cigarettes per day (CPD). Smoking reduction percentage was measured by dividing OTI cigarettes/day at the particular time point (e.g., 15 weeks or 12 months) by OTI cigarettes/day at baseline, multiplied by 100; with complete smoking cessation classified as 100% smoking reduction. Likewise, if the number of cigarettes smoked stayed the same or increased from baseline then the individual was classified as zero percent reduction.

### **2.2.5. Nicotine replacement therapy use, diet and exercise measures**

For the first six months of the study, all participants had access to NRT. In the analysis, participants were coded as either having used NRT, or not having used NRT.

An overall unhealthy eating index (diet score) was also created, with 1 point given for an answer to each question that indicated unhealthy eating habits. The

index ranged from 0-12, with higher scores indicating more unhealthy eating habits. Unhealthy eating habits included: non-optimal servings per day of each of the five food groups (e.g., fruit, vegetables, breads, lean meats, and dairy); high fat or high sugar foods; choosing non-wholegrain products; consumption of full sugar soft drinks or cordials; missing breakfast; adding salt to food; using full fat dairy. Exercise was measured in walking minutes per week.

#### **2.2.6. *Treatment***

Participants received either (a) a face-to-face multi-component 'Healthy Lifestyle' intervention for smoking cessation and cardiovascular (CVD) risk reduction (NRT plus a total of 17 sessions consisting of the initial 90-minute common session then seven further one hour weekly sessions, plus three fortnightly hour long sessions and monthly 'booster' sessions of one hour duration for six months); or (b) a predominantly telephone-based, less intensive intervention focusing mainly on monitoring use of NRT and CVD risk behaviours, and delivered at the same intervals as the Healthy Lifestyles intervention condition. Telephone-based sessions were scheduled to be approximately 10 minutes duration and at weeks 4, 8, and 15; participants attended 30-minute face-to-face sessions where NRT was dispensed.

#### **2.3. Statistical Analyses**

Data were analysed using SAS 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics are presented by counts and percentages for categorical variables and means (standard deviation) or median (min, max, interquartile range) for

continuous variables. Comparisons of categorical variables were performed using chi-square tests. Changes in suicidality, depression and amount smoked over time (baseline, 15 weeks, and 12 months) were assessed using linear mixed modelling to account for repeated measures within subjects. The association between each suicidality measure (outcome) and treatment group over time was tested using mixed modelling (2-way ANOVA), including group, time and an interaction term (group \* time).

Mediation analysis was used to determine whether the relationship between smoking reduction and suicidality was mediated through depression. Baron and Kenny's (1986) methodology was followed, and the SAS macro "Indirect" was used to implement these methods (Preacher and Hayes, 2008). Estimates were calculated for the total effect of smoking reduction on suicidality, the effect of smoking reduction on depression and the effect of depression on suicidality adjusting for smoking reduction. Bootstrapping was used to create confidence intervals (CIs), allowing us to determine whether the relationship had been significantly reduced with the inclusion of the mediator. The percentage of the effect that could be explained by the mediator (indirect effect) was measured by the formula:  $(\text{total effect} - \text{direct effect}) / (\text{total}) * 100$ .

Mediation analyses were adjusted for confounders, as determined *a priori*, that were thought to potentially effect the association between smoking cessation and depression or the association between depression and suicidal ideation (BPRS

item). For all models, the effects are presented as estimates ( $\beta$  coefficients) with 95% confidence intervals for the linear regressions, and as percentage of effect size represented by the mediation variable for the mediation analysis. We present Wald p-values for tests of statistical significance, using a 5% significance level.

### 3. Results

The results from the full Healthy Lifestyles study are presented in full in Baker et al (2015). In summary, there were no significant differences between the two intervention conditions in CVD risk or smoking outcomes at 15 weeks or 12 months, with improvements in both conditions (e.g., 12 months: 6.4% confirmed point prevalence abstinence rate; 17% experiencing a 50% or greater smoking reduction; mean reduction of 8.6 cigarettes per day; mean improvement in GAF of 9.8 points) (Baker et al, 2015). Smoking reduction rates were higher among those who attended more treatment sessions (e.g., among those attending 9-17 sessions, 25% experienced a 50% or greater smoking reduction at 12 months) (Baker et al, 2015).

Baseline demographic characteristics, mental illness and treatment related variables are reported in Table 1. There was no significant association between suicidality and treatment group over time ( $p=0.871$ ); therefore, all subsequent analyses were conducted across treatment groups.

- **Change in suicidality, depression and cigarette smoking over time**

Using linear mixed modelling, mean changes over time were significant for all measures. Mean suicide score improved over time ( $\beta = -0.017$ ,  $p = 0.025$ ), number of cigarettes per day reduced over time ( $\beta = -0.712$ ,  $p < 0.001$ ) and depression scores improved over time ( $\beta = -0.338$ ,  $p < 0.001$ ). The majority of participants reported no suicidality at baseline, 15 weeks and 12 months (70-74%; Table 2).

Overall, the median change in suicidality at both 15 weeks and 12 months was 0 points (IQR 0-0). When participants who had no suicidality at baseline were removed, the median (IQR) change was -1 (-2 to 0) at 15 weeks and -1 (-2 to -1) at 12 months, indicative of reduced levels of suicidality. At 12 months, 11% of the retained sample had successfully abstained from smoking ( $n = 15$  (10.79%) confirmed seven day point prevalence abstinence).

- ***Mediation Analysis***

Figure 1 displays the results of the adjusted linear regression models at 12 months examining whether percent smoking reduction was a significant predictor of suicidality. Adjusted models included the following demographic and lifestyle variables: age, gender, diet score, walking minutes per day, lifetime psychiatric

diagnosis, alcohol use, cannabis use, Global Assessment of Functioning, history of suicide attempts, number of sessions attended and any NRT use.

As shown in Figure 1, smoking reduction was significantly associated with suicidality change (total effect,  $p=0.007$ ), and an association was found between smoking reduction and depression ( $p=0.078$ ) as well as between depression and suicidality ( $p<0.001$ ).

After adjusting for depression, the association between smoking reduction and suicidality was reduced but remained statistically significant (direct effect,  $p=0.034$ ); bootstrapped CI estimates for the indirect (total minus direct) effect also indicated that there was some evidence of mediation of the association of smoking reduction and suicidal ideation through depression ( $\beta = -0.0024$ , CI -0.001 to  $<0.0001$ ) at 12 months. The percentage of the total effect that was mediated through depression was  $(-0.002 / -0.008) * 100 = 30\%$ . Overall, variables in the adjusted model described 39.1% of the variance in the suicidality outcome ( $R^2 = 0.409$ ). Mediation through depression accounted for 12.3% of this overall variance (i.e., 30% of 40.9%).

At 15 weeks, smoking reduction was not significantly associated with suicidal ideation, either through the total effect ( $p=0.901$ ) or when mediated via depression (direct effect,  $p=0.907$ ). Bootstrapped CI estimates for the indirect effect indicated that there was no evidence of mediation of the association of

smoking reduction and suicidal ideation through depression at 15 weeks ( $\beta=0.007$ , CI -0.002 to 0.004).

#### 4. Discussion

This sub-study aimed to identify the effects of smoking reduction on suicidality measures in participants with SMI. We employed data from 235 smokers with psychosis who participated in a Healthy Lifestyles intervention trial and were followed over 12 months. Among this cohort suicidal ideation scores decreased with reductions in smoking; thus, there was a small positive association between smoking reduction and improvements in suicidality. However, this was found only at 12 months follow up and not at 15 weeks (mid-intervention). Further, we found that the association was reduced when depression was also included in the modelling. However, the estimated effect of depression on suicidality was 30%, indicating that not all of the suicidality associated with smoking was related to or mediated by depression.

These findings have potentially important implications. It is recognised that smoking could be related to an increase in depression (Boden et al, 2010) and smoking cessation is associated with reduced depression (Taylor et al, 2014). Further, smoking and depression share common biochemical (Malone et al, 2003) and neurocognitive abnormalities such as cognitive inflexibility (Deveney and Deldin, 2006; Miranda et al, 2012; Connor and Nock, 2014) that have been shown to be associated with suicidality.



However, it is likely that other biological or biochemical changes associated with smoking such as orbito-frontal cortical (OFC) thinning (Kuhn et al, 2010) and/or biochemical changes such as lower serotonin (Malone et al, 2003) may also mediate suicidality. Emerging evidence has shown an association between frontal cortical dysfunction and suicidal risk in patients with schizophrenia (Minzenberg et al, 2014; 2015). Further, Durazzo et al (2010), have reviewed the literature on the neurocognitive and neurobiological changes associated with chronic smoking and concluded that chronic smokers are more likely to exhibit executive dysfunctions including cognitive inflexibility and atrophy involving anterior frontal regions. Lesion studies have demonstrated that emotion recognition and other social cognitive abilities depend critically on the orbitofrontal cortex (Heberlein et al, 2008), while suicidal behaviours, aggression, impulsivity and smoking have all been linked to a reduced central serotonin or “low serotonin syndrome” (Malone et al, 2003). Taken together, these findings suggest that chronic smoking is associated with neurobiological and neurocognitive changes that are in turn associated with increased suicidal risk.

What is particularly interesting is that recent research indicates that smoking-associated brain changes may be reversible upon cessation (Karama et al, 2015). It is therefore possible that smoking can induce brain changes that are associated with suicidality, but these changes are reversible over time with smoking cessation.

We had the opportunity to study the effects of a healthy lifestyle intervention on suicidality measures in real time and also to study the impact of smoking reduction over a period of 12 months. We were also able to undertake a mediation analysis and to adjust for a number of important covariates that could account for changes in suicidality over time including age, gender, diet, walking time per week, life-time psychiatric diagnosis, alcohol use, cannabis use, current functioning, history of suicide attempts, number of sessions attended and any NRT use.

This sub-study has some clear limitations. We used a single item clinician-rated suicidal measure, item 4 of the BPRS to measure suicidality. It should be noted, however, that this has been used to measure suicidality in previous research (Marcinko et al, 2008) and single suicidal item measures have been shown to be valid in clinical studies (Desseilles et al, 2012).

In addition, only a small proportion of participants were known to have stopped smoking at 15 weeks (26/235, 11.1%) and 12 months (15/235, 6.4%). This being a sub-study of a multi-component healthy lifestyles intervention among individuals with severe mental illness, it was not powered to study the effect of smoking cessation on suicidality measures. Much larger studies would be needed in order to do this. It is recommended that suicidality be routinely

measured in smoking cessation studies and results potentially be pooled across studies.

We did not include measures such as impulsivity that might also explain changes in suicidality. We also did not adjust for severity of illness, psychopharmacology or examine the effects of coping strategies and/or other cognitive or problem solving difficulties, factors that are known to influence the association between mental illness and smoking and mental illness and suicide.

We studied only suicidal ideation and intent and not completed suicide. While suicidal behaviours are doubtlessly an important “predictor” of future suicide, the predictive capabilities are limited as suicide is rare. However, Chapman et al (2015), in a recent meta-analysis, found a strong association (OR 6.49, 95% CI 3.82-11.02) for suicidal ideation and later suicide in patients with schizophrenia spectrum psychosis.

Data on suicidal risk reduction in patients with severe mental illness is at best confusing. For example, while poor adherence with antipsychotic medication is associated with a 37-fold increased risk of suicide (Hor and Taylor, 2010), the evidence base for antipsychotic medication (with the exception of clozapine) in reducing suicidal risk is still unclear (Aguilar and Siris, 2007). In general, studies that have explored effectiveness of psychosocial interventions in reducing suicide risk among psychotic patients have shown mixed results (Donker et al, 2013).

There is therefore a need for more studies that look at alternate strategies; such studies would be relevant if they sought to address or modify highly prevalent behaviours (such as smoking), which in turn increase suicidal risk. We recently calculated the suicidal burden associated with smoking in a sample of Australian patients with psychosis; smoking contributed to 21% of suicidal behaviours in that sample (Sankaranarayanan and Castle, 2016). Thus it is conceivable that strategies that aim to reduce or promote smoking cessation in people with psychosis should result in reduction in suicidality. As far as we are aware, this is the first study to have explored the impact of smoking cessation treatment on suicidality among people with SMI.

## **5 Conclusion:**

In conclusion, we found that smoking reduction was associated with reduction in suicidal ideation among individuals with psychosis. In addition to physical health impacts, the results of the present study provide a further important reason why clinicians should address smoking in this population. There is a need for further research to confirm the findings of our study.

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### **Contributors**

All authors contributed to the writing of this manuscript. Analysis was performed by the second and fourth authors, all authors contributed to the interpretation of the results. Drafting of the manuscript was performed by the first author and contributed by the remaining authors.

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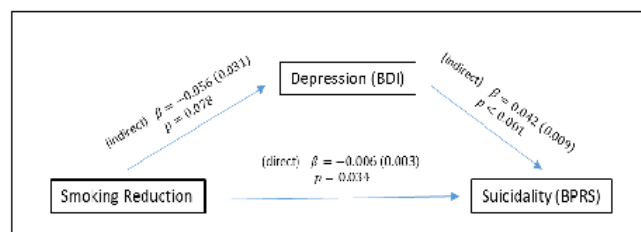


Figure 1. Mediation (linear regression) analysis showing association of smoking reduction, depression and suicidality change; 12 months

Table 1: *Demographic characteristics, mental illness, and smoking cessation treatment related variables at baseline.*

Demographic Characteristic	Total (N= 235)	Mental Health and Medication Characteristics	Total (N= 235)
Age (mean, SD)	42 (11)	Diagnosis	
Gender (Male)	138(59%)	Schizophrenia spectrum disorder	138 (59%)
Education		Psychosis (not otherwise specified)	45 (19%)
Left school, no qualifications	53 (24%)	Bipolar affective disorder	52 (22%)
Secondary school qualifications	54 (25%)	Age of onset (mean, SD)	23 (9)
Diploma/certificate	86 (39%)	Duration of psychosis	
Tertiary Education	26 (12%)	< 1 month	5 (2.5%)
BMI >25	184 (81%)	> 1 month, < 6 months	24 (12%)
Walking (minutes per week; median, Q1-Q3)	140 (45-210)	> 6 months	173 (86%)
Diet score (unhealthy eating index; mean, SD)	5.9 (1.8)	Psychotropic medications	
Alcohol use		Antipsychotics	205 (92.7%)

No use	120 (55%)	Atypical	181 (88%)
Within guidelines	70 (32%)	Typical	24 (12%)
Over guidelines/Excessive	28 (13%)	Antidepressant and mood stabilizer	136 (61.5%)
Cannabis use	18 (8.2%)	Anxiolytic	33 (14.9%)
NRT use	181 (86%)	Agent used in drug dependence	7 (3.2%)
Number of treatment sessions		SF-12 Quality of life- Physical score (mean, SD)	43 (11.4)
Low (1-3 sessions)	41 (19%)	SF-12 Quality of life- Mental score (mean, SD)	41.3 (12.1)
Midrange (4-8 sessions)	36 (17%)	Global Assessment of Functioning (mean, SD)	51.2 (10.8)
High (9-17 sessions)	134 (64%)	Past suicide attempt (ever)	120 (56%)
Treatment		Brief psychiatric rating scale (total; mean, SD)	42.6 (12.9)
Face to face therapy	122 (52%)	Beck depression inventory (total; mean, SD)	17.4 (12.8)
Telephone	113 (48%)		

**Table 2. Smoking, suicidality and depression measures**

Parameter	Time-points			Regression	
	Baseline (n = 235)	15 weeks (n = 165)	12 months (n = 139)	$\beta$ estimate	P value
Suicidity (BPRS)					
No suicidity	153 (70%)	117 (73%)	90 (74%)		
Very mild	26 (12%)	12 (7.5%)	18 (15%)		
Mild	19 (8.7%)	12 (7.5%)	18 (15%)		
Moderate	12 (5.5%)	9 (5.6%)	6 (4.9%)		
Moderate severe	6 (2.7%)	6 (3.8%)	1 (0.8%)		
Severe	2 (0.9%)	-	-		
Extremely severe	1 (0.5%)	1 (0.6%)	-		
Mean (SD)	1.6 (1.2)	1.6 (1.2)	1.4 (0.9)	-0.02	0.025
Smoking (CPD; Mean, SD)	28.2 (14.6)	13.4 (12.0)	18.2 (13.7)	-0.71	<0.001
Depression (mean, SD)	17.4 (12.8)	15.3 (12.6)	12.8 (11.7)	-0.34	<0.001

#### Highlights

- This study explored impact of smoking reduction on suicidality among people with psychosis
- At 12 months, smoking reduction was significantly associated with reduction in suicidality.

- At 12 months, smoking reduction was significantly associated with reduction in depression
- Association between smoking and suicidality change remained statistically significant after adjusting for depression
- Depression accounted for only 30% of suicidality associated with smoking.