Smoking, symptoms, and quality of life in patients with psychosis, siblings, and healthy controls: a prospective, longitudinal cohort study

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Summary

Background The self-medication hypothesis postulates that the high prevalence of smoking in patients with psychosis can be explained by the ameliorating effect of smoking on symptoms. However, there are few large prospective studies testing this hypothesis. We aimed to examine the multi-cross-sectional and prospective associations of changes in smoking behaviour with symptoms and quality of life.

Methods In this prospective cohort study we recruited patients with a non-affective psychosis (n=1094), unaffected siblings (n=1047), and healthy controls (n=579). Patients aged between 16 and 50 years and diagnosed with a non-affective psychosis according to DSM-IV were recruited by clinicians from four university medical centres and 36 associated mental health-care institutions in the Netherlands and Belgium between Jan 13, 2004, and March 6, 2014. Smoking status and number of cigarettes per day were assessed at baseline, and at 3-year and 6-year follow-up using the Composite International Diagnostic Interview (CIDI). Symptom frequency was self-rated with the Community Assessment of Psychotic Experience (CAPE), and quality of life was assessed by the WHO Quality of Life (WHOQOL) schedule. Multiple linear mixed-effects regression analyses were done accounting for multiple confounders.

Findings At baseline, 729 (67%) of 1094 of patients smoked (mean 17·5 cigarettes per day, SD 8·8) compared with 401 (38%) of 1047 siblings and 145 (25%) of 579 healthy controls. Multi-cross-sectional results of linear mixed-effects analyses showed that smoking in patients and siblings was associated with more frequent positive symptoms (estimate 0·14, SE 0·02, p<0·0001 in patients; 0·03, 0·01, p=0·0019 in siblings), negative symptoms (0·15, 0·03, p<0·0001 in patients; 0·09, 0·02, p<0·0001 in siblings), and depressive symptoms (0·12, 0·03 p<0·0001 in patients; 0·08, 0·02 p<0·0001 in siblings) and lower quality of life (–0·59, 0·11, p<0·0001 in patients; –0·31, 0·09, p=0·0002 in siblings) than non-smokers. In controls, smoking was associated with significantly higher frequency of subclinical positive symptoms (0·03, 0·01, p=0·0016) and depressive symptoms (0·05, 0·03, p=0·0432) than in participants who did not smoke. Patients who started to smoke during follow-up showed a significant increase in self-reported symptoms, particularly positive symptoms (0·161, 0·077, p=0·0381), whereas smoking cessation was not associated with changes in symptoms or quality of life compared with those who showed no change in smoking behaviour. Similar results were obtained for the changes in the number of cigarettes smoked.

Interpretation Our findings do not empirically support the self-medication hypothesis. The absence of long-term symptomatic relief from smoking should encourage clinicians to help patients with psychosis to quit smoking.

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See Online for appendix

Introduction

Smoking is a risk factor for increased somatic morbidity and mortality in the general population and psychiatric patients. Smoking is consistently found to be more prevalent in patients with psychosis than in the general population.[1] Tobacco use has declined during the past decades in the high-income countries, but the prevalence of smoking in patients with psychosis remains alarmingly high. Self-medication is a popular hypothesis to explain the high prevalence of smoking in patients with psychiatric disorders. The hypothesis postulates that patients with psychosis derive symptomatic relief from

Research in context

Evidence before this study

The nature of the relationship between smoking and symptoms in patients with a psychotic disorder is highly debated. According to the self-medication hypothesis, patients smoke cigarettes to weaken their symptoms, which explains the high frequency of smoking in this population. We searched PubMed to review studies that tested this hypothesis—ie, studies comparing smoking with non-smoking patients with a psychotic disorder, measuring symptoms and quality of life, or both. We searched on Feb 23, 2018, and updated the search on June 26, 2018, using the following search string: (schizophreni* OR psychosis*) AND (smoking* OR smoking cessation OR cigarettes OR tobacco*) AND (psychopathology OR symptomatology OR "Mental Health" [Mesh] OR depressive OR "Quality of Life"[Mesh]). Resulting studies have shown contradictory findings. However, there are few large prospective studies with patients with psychosis starting or quitting smoking and thus no conclusion could be drawn.

Added value of this study

This large study uses prospective multi-cross-sectional and long-term data to test the self-medication hypothesis. Smoking showed a multi-cross-sectional association with more psychotic and depressive symptoms and lower quality of life in patients, siblings, and controls, than non-smoking. Importantly, patients who started to smoke during our study developed more positive, negative, and depressive symptoms after they had started smoking than did those who did not change their smoking behaviour. Additionally, an increase in the number of cigarettes per day was associated with an increase in self-rated symptoms and with a decrease in quality of life in patients, siblings, and controls. In patients, we found no associations between change in smoking status and clinician-rated symptoms and no associations between smoking cessation and symptoms and quality of life.

Implications of all the available evidence

The long-term results of our study do not support the self-medication hypothesis of smoking in patients with psychosis. This finding is consistent with most of the existing evidence from smaller studies. Clinicians should be aware that starting to smoke or smoking more cigarettes per day does not reduce long-term self-rated symptoms in patients with a psychotic disorder and that smoking cessation is not associated with worsening of symptoms in these patients. Future research is required to examine the alternative explanations of the high prevalence of tobacco smoking in patients with psychosis.

tobacco smoking,[2,3] and assumes an association between smoking and effects on symptoms, cognitive functioning, quality of life, and side-effects of psychotropic medication. Although the self-medication hypothesis is still frequently reported as valid, there is not much evidence that cigarette smoking reduces symptoms (frequency and severity). So far, conflicting results have emerged regarding cross-sectional differences in symptoms or quality of life between smoking and non-smoking patients with a psychotic disorder. One long-term study reported that the number of cigarettes only covaried with depression scores over time.[4] Another cohort study reported no differences over time between smoking and non-smoking patients with psychosis in symptom severity and functioning.[5] The authors of a systematic review on the course of symptoms and smoking in patients with psychosis concluded that, because of the scarcity of large, prospective studies, no definite conclusion could be drawn.[6]

Therefore, we aimed to examine: the multi-cross-sectional associations between smoking and clinical and subclinical psychotic and depressive symptoms and quality of life; and the long-term associations between changes in smoking status and changes in symptoms and quality of life in a large prospective study of patients with a psychotic disorder, non-affected siblings, and healthy controls. According to the assumptions of the self-medication hypothesis, we formulated several hypotheses. We expected that: smoking in patients with a psychotic disorder would be negatively associated with symptoms and positively with quality of life; starting to smoke would be associated with a reduction in symptoms and an improvement in quality of life; and smoking cessation would be associated with an increase in symptoms and reduced quality of life. In control participants and siblings, who are prone to similar genetic and environmental vulnerabilities as patients but do not have illness-related factors, we expected to find no association between change in smoking behaviour and subclinical symptoms or quality of life.

Methods

Study design and participants

This study was done within the naturalistic, multicentre cohort study of the Genetic Risk and Outcome of Psychosis (GROUP). The total sample consisted of 1119 patients with a diagnosis in the non-affective psychotic spectrum, 920 parents, 1059 unaffected siblings, and 586 unrelated healthy controls. Study design, power calculations, recruitment procedure, and baseline characteristics of participants have been described in detail in a separate paper.[7] Patients aged between 16 and 50 years and diagnosed with a non-affective psychosis according to the DSM-IV[8] were recruited by clinicians from four university medical centres and 36 associated mental health-care institutions in the Netherlands and Belgium between Jan 13, 2004, and March 6, 2014. Siblings and controls were included if non-affected with a psychotic disorder. All patients, unaffected siblings, and controls took part in the baseline

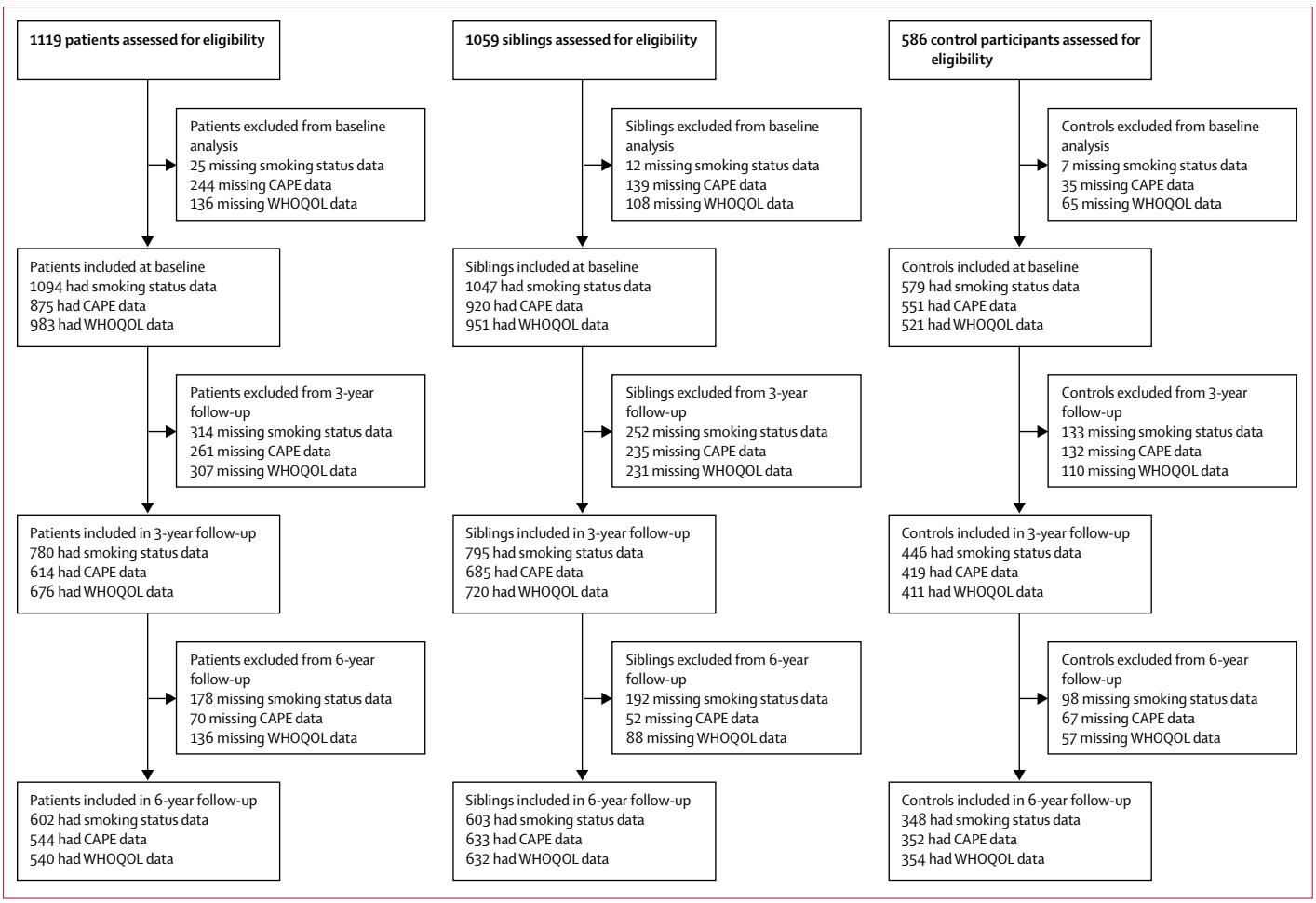

Figure: **Study profile**
CAPE=Community Assessment of Psychic Experience. WHOQOL=WHO Quality of Life.

assessment and were invited for follow-up assessments at 3 years and 6 years after inclusion. Participants were included in the study if they had complete data for the baseline measurement of smoking. The GROUP was approved by the medical ethics committee of the Academic Medical Center of Utrecht. Written informed consent was obtained before inclusion.

Procedures

We administered the Composite International Diagnostic Interview (CIDI)[9] to assess the quality, severity, and course of tobacco use during the past year. The CIDI substance abuse module (CIDI-SAM) covers tobacco in considerable detail and was found to be reliable in a cross-cultural trial.[10] Participants were defined as smokers if they smoked daily during 1 month or longer in the past 12 months. Data were also collected about the number of cigarettes per day in the period of most severe smoking in the past 12 months.

Patients, siblings, and controls self-rated frequency of symptoms using the Community Assessment of Psychic Experience (CAPE).[11] CAPE is a self-report questionnaire to assess psychotic and depressive experiences. Each of the items is rated in terms of frequency on a scale from 0 (absent) to 3 (almost always). A mean total score was calculated for the subscales positive symptoms (if at least 14 of 20 items were available), negative symptoms (if at least nine of 14 items were available), and depressive symptoms (if at least five of eight items were available). Furthermore, quality of life was assessed with the WHO Quality of Life-BREF (WHOQOL-BREF) questionnaire that has previously been validated in a Dutch adult psychiatric population.[12,13] This self-report scale assesses quality of life in four domains (physical, psychological, social, and environmental); we used the total scores of the mean per domain (range 4–20). To validate the self-rated outcomes in patients, we also used an interviewer-rated tool to assess symptom severity in patients by administering the Positive And Negative Syndrome Scale (PANSS).[14] The PANSS is a 30-item interview with items rated on a seven-point scale; total scores of dimensions were calculated following methods of van der Gaag and

	Patients (n=1094)			Siblings (n=1047)			Control participants (n=579)		
	Smoking	Non-smoking	p value*	Smoking	Non-smoking	p value†	Smoking	Non-smoking	p value
Number	729 (67%)	365 (33%)	..	401 (38%)	646 (62%)	..	145 (25%)	434 (75%)	..
Age	26·8 (6·9)	29·2 (9·5)	<0·0001	27·5 (8·1)	28·1 (8·4)	0·2388	26·9 (9·9)	30·7 (10·8)	0·2534
Education	12·0 (3·7), n=683	13·2 (3·9), n=335	<0·0001	12·8 (3·9), n=386	13·9 (4·0), n=626	<0·0001	14·2 (3·0), n=142	14·6 (3·4), n=422	0·1360
Cigarettes per day	17·5 (8·8), n=729	0 (0), n=365	<0·0001	12·6 (8·1), n=400	0 (0), n=646	<0·0001	11·9 (7·8), n=145	0 (0), n=434	<0·0001
PANSS‡									
Positive symptoms	14·6 (6·8), n=678	12·6 (5·9), n=335	<0·0001	..	..	..	..	..	..
Negative symptoms	15·2 (6·8), n=675	14·6 (6·2), n=327	0·2310	..	..	..	..	..	..
Emotional distress	16·3 (5·8), n=686	14·9 (5·4), n=335	0·0003	..	..	..	..	..	..
CAPE§									
Positive symptoms	0·72 (0·50), n=582	0·58 (0·45), n=293	0·0001	0·23 (0·22), n=347	0·19 (0·19), n=573	0·0120	0·22 (0·17), n=141	0·18 (0·17), n=410	0·0398
Negative symptoms	1·06 (0·55), n=582	0·94 (0·50), n=293	0·0013	0·62 (0·40), n=347	0·51 (0·37), n=573	<0·0001	0·53 (0·34), n=141	0·47 (0·31), n=410	0·0502
Depressive symptoms	1·03 (0·58), n=584	0·95 (0·57), n=295	0·0707	0·69 (0·43), n=348	0·60 (0·38), n=574	0·0013	0·64 (0·36), n=141	0·57 (0·34), n=410	0·0462
WHOQOL total score	13·2 (2·3), n=649	14·1 (2·2), n=334	<0·0001	16·0 (1·8), n=352	15·5 (2), n=599	0·0002	16·0 (1·75), n=134	16·3 (1·58), n=387	0·0886
Duration of illness	4·2 (3·8), n=681	4·3 (4·0), n=329	0·5998	..	..	..	..	..	..
GAF	55·0 (16·3), n=657	57·8 (15·3), n=318	0·0090	..	..	..	..	..	..
Sex									
Male	603 (83%)	230 (63%)	<0·0001	198 (49%)	281 (43%)	0·073	73 (50%)	193 (44%)	0·2573
Female	126 (17%)	135 (37%)		203 (51%)	365 (57%)		72 (50%)	241 (56%)	
Tested positive for cannabis	147/640 (23%)	7/320 (2%)	<0·0001	62/355 (17%)	11/594 (2%)	<0·0001	19/139 (13%)	8/413 (2%)	<0·0001
Antipsychotic drug use	615/647 (95%)	300/324 (93%)	0·1210	..	..	..	..	..	..

Data are n (%) or mean (SD), n. PANSS=Positive and Negative Syndrome Scale. CAPE=Community Assessment of Psychic Experience, frequency subscales. GAF=Global Assessment of Functioning. WHOQOL= WHO Quality of Life. *Two-sided p values were computed by a *t* test. †Two-sided p-values were computed by a Pearson's χ^2 test. ‡Three PANSS factors were used: positive symptoms factor (1–55), the negative symptoms factor (2–62), and the emotional distress factor (8–56). §A total score of the mean of approximately 70% of the items representing positive symptoms (20 items), negative symptoms (14 items), and depressive symptoms (8 items) was calculated.

Table 1: **Baseline characteristics of smoking and non-smoking patients with psychosis, siblings, and controls**

colleagues.[15] Three of five available dimensions were used to describe the severity of positive symptoms (range 1–55), negative symptoms (range 2–62), and emotional distress (range 8–56).

Covariates

A priori, age and sex were selected as potential confounders for all analyses. In sensitivity analyses, cannabis use, years of education as a proxy for socioeconomic status, antipsychotic medication use, and level of functioning were added as covariates to the model because these variables might be associated with smoking and with symptoms or quality of life.[4] Cannabis use was assessed with urinalysis. Urine was screened for the presence of cannabis with a 50 ng/mL THC cutoff to infer a detection window of 1 month. Age, sex, or current use of antipsychotic medication, and the Global Assessment of Functioning (GAF) scale with the subscale psychopathology[8] were assessed at each measurement.

Statistical analysis

We made cross-sectional baseline comparisons between smokers and non-smokers with Student's *t* test and χ^2 test in patients, siblings, and healthy controls. We used R version 3.3.2 and the lme4 package to perform linear mixed-effects analyses for the association of smoking status with symptoms and quality of life, in line with a similar study regarding cognitive functioning within this sample.[16] We did not apply missing value imputation but fitted mixed-effects models using restricted maximum likelihood (REML). Visual inspection of residual plots of the dependent variable revealed deviations from normality. We compared the results of linear mixed-effects models after log transformation and square root transformation

of the dependent variable. Additionally, we applied robust mixed-effects models without transformation of the dependent variable. Unfortunately, using the optimiser of robust mixed-effects models within the R package robustlmm led to non-convergence of our model when we added the by-subject random slope "time" to the models. Since the results of the untransformed, transformed, and robust models were similar with respect to the estimates and *t* values of the parameter of interest, we chose to report only results of the linear mixed-effects models without transformation of the dependent variable. p values were calculated by the Kenward-Roger or Satterthwaite approaches while using the pbkrtest package, which have been evaluated in REML-fitted models and produced the most acceptable type I error rates in mixed-effects models.[17] We used a significance level of 0·05 (two-tailed) for all analyses. Release 6.00 of the GROUP database was used for the analyses.

Between-group differences in the association between smoking and all outcomes were tested in linear mixed models with a participant status*smoking status interaction variable as a fixed effect and an extra random intercept for family level. Because these models showed significant differences between patients and controls for all outcomes except the depression subscale of CAPE, but sometimes failed to converge, further analyses were fitted for each group separately (appendix). To examine the first aim (multi-cross-sectional associations between smoking and clinical and subclinical psychotic and depressive symptoms and quality of life), we entered smoking status (smoker or non-smoker), time, age, and sex as fixed effects into the first set of models for patients, siblings, and controls. As random effects, we added intercepts for subjects and by-subject random slopes for the effect of time. Each variable was added in a forward approach and Akaike information criterion (AIC) was used to compare model fit.

Participants were included in the multi-cross-sectional analyses if data were available for at least one timepoint (baseline, 3 years, or 6 years) on the outcome variable of interest and for smoking behaviour because mixed modelling allowed us to calculate valid estimates under the assumption of missing at random even if data for one or two timepoints were missing. As sensitivity analyses, a second set of models was run with the number of cigarettes per day as a predictor, instead of smoking status. To investigate whether the association could be distorted by influential outliers, subset analyses were done in patients who smoked 40 or fewer and 30 or fewer cigarettes per day for all outcomes of interest. The estimates and significance levels of the variables of interest were similar (data not shown). To assess the potential effect of confounders, cannabis use and years of education were added as covariates to a third set of models in siblings and controls. For the patient models, we also added antipsychotic medication and level of functioning. We ran the first models about self-rated symptom frequency once more, but with clinician-rated PANSS dimensions capturing symptom severity.

	Patients (n=1094)	Siblings (n=1047)	Control participants (n=579)
CAPE: frequency of positive symptoms (0–3)			
Intercept	0·565 (0·025), p<0·0001	0·188 (0·009) p<0·0001	0·181 (0·010), p<0·0001
Smoking	0·140 (0·024), p<0·0001	0·030 (0·008), p=0·0019	0·033 (0·010), p=0·0016
3-year follow-up	−0·137 (0·019), p<0·0001	−0·084 (0·007), p<0·0001	−0·092 (0·007), p<0·0001
6-year follow-up	−0·189 (0·022), p<0·0001	−0·092 (0·008), p<0·0001	−0·100 (0·009), p<0·0001
CAPE: frequency of negative symptoms (0–3)			
Intercept	0·903 (0·028), p<0·0001	0·493 (0·019), p<0·0001	0·461 (0·020), p<0·0001
Smoking	0·145 (0·027), p<0·0001	0·094 (0·018), p<0·0001	0·042 (0·023), p0·0657
3-year follow-up	−0·090 (0·021), p<0·0001	−0·079 (0·014), p<0·0001	−0·085 (0·015), p<0·0001
6-year follow-up	−0·149 (0·026), p<0·0001	−0·056 (0·017), p=0·0013	−0·076 (0·019), p<0·0001
CAPE: frequency of depressive symptoms (0–3)			
Intercept	0·850 (0·029), p<0·0001	0·508 (0·019), p<0·0001	0·489 (0·023), p<0·0001
Smoking	0·120 (0·028), p<0·0001	0·078 (0·018), p<0·0001	0·053 (0·026), p=0·0432
3-year follow-up	−0·123 (0·022), p<0·0001	−0·117 (0·014), p<0·0001	−0·142 (0·017), p<0·0001
6-year follow-up	−0·147 (0·026), p<0·0001	−0·010 (0·017), p<0·0001	−0·129 (0·022), p<0·0001
WHOQOL total score (4–20)			
Intercept	13·730 (0·113), p<0·0001	16·038 (0·093), p<0·0001	16·269 (0·106), p<0·0001
Smoking	−0·594 (0·110), p<0·0001	−0·309 (0·085), p=0·0002	−0·126 (0·118), p=0·2804
3-year follow-up	0·773 (0·079), p<0·0001	0·311 (0·062), p<0·0001	0·3147 (0·070), p<0·0001
6-year follow-up	0·801 (0·100), p<0·0001	0·205 (0·077), p=0·008	0·2981 (0·088), p=0·0008

Data are estimate (SE). P values were calculated with the Kenward-Roger approach, or the Satterthwaite approach if the Kenward-Roger approach was not possible. The fixed effects entered into the models were smoking, age, time, and sex. Baseline assessment was set as reference. As random effects, intercepts for participants were added and by-subject random slopes for the effect of time. CAPE=Community Assessment of Psychic Experience. WHOQOL= WHO Quality of Life.

Table 2: **Results of linear mixed models regarding the multi-cross-sectional association between smoking status and self-rated frequency of symptoms and quality of life corrected for sex and age**

To examine the second aim (the prospective long-term associations between changes in smoking status and changes in symptoms and quality of life), we identified change in smoking status over a 3-year follow-up period (eg, 3-year *vs* baseline, and 6-year *vs* 3-year follow-up). Similarly, a change score was calculated between these timepoints for symptoms and quality of life. In case of missing data in one or both of the compared measurement waves, the change score was set as missing. Changes scores were not computed if 6-year and baseline data but no 3-year data were available. Subsequently, we ran similar models with the same fixed and random effects as described above.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Results

1094 patients, 1047 siblings, and 579 controls had baseline data on their smoking status (figure). All patients were diagnosed with a non-affective psychotic disorder, of whom 717 (66%) of 1094 had a diagnosis of schizophrenia

	Patients (n=1094)	Siblings (n=1047)	Control participants (n=579)
CAPE: frequency of positive symptoms (0–3)			
Intercept	0·590 (0·022), p<0·0001	0·185 (0·009), p<0·0001	0·182 (0·010), p<0·0001
Cigarettes per day	0·006 (0·001), p<0·0001	0·002 (0·001), p<0·0001	0·002 (0·001), p=0·0027
3-year follow-up	−0·141 (0·019), p<0·0001	−0·084 (0·007), p<0·0001	−0·092 (0·007), p<0·0001
6-year follow-up	−0·199 (0·022), p<0·0001	−0·091 (0·008), p<0·0001	−0·100 (0·009), p<0·0001
CAPE, frequency of negative symptoms (0–3)			
Intercept	0·924 (0·024), <0·0001	0·490 (0·019), p<0·0001	0·459 (0·020), p<0·0001
Cigarettes per day	0·006 (0·001), p<0·0001	0·007 (0·001), p<0·0001	0·004 (0·002), p=0·0129
3-year follow-up	−0·972 (0·021), p<0·0001	−0·079 (0·014), p<0·0001	−0·085 (0·015), p<0·0001
6-year follow-up	−0·156 (0·026), p<0·0001	−0·057 (0·017), 0·0009	−0·075 (0·019), p<0·0001
CAPE, frequency of depressive symptoms (0–3)			
Intercept	0·851 (0·026), p<0·0001	0·504 (0·019), p<0·0001	0·487 (0·021), p<0·0001
Cigarettes per day	0·007 (0·001), p<0·0001	0·007 (0·001), p<0·0001	0·003 (0·001), p=0·0552
3-year follow-up	−0·128 (0·023), p<0·0001	−0·116 (0·014), p<0·0001	−0·142 (0·015), p<0·0001
6-year follow-up	−0·155 (0·026), p<0·0001	−0·099 (0·017), p<0·0001	−0·109 (0·020), p<0·0001
WHOQOL total score (4–20)			
Intercept	13·736 (0·099), p<0·0001	16·066 (0·092), p<0·0001	16·288 (0·104), p<0·0001
Cigarettes per day	−0·034 (0·0040), p<0·0001	−0·028 (0·005), p<0·0001	−0·017 (0·009), p=0·0411
3-year follow-up	0·800 (0·079), p<0·0001	0·306 (0·062), p<0·0001	0·307 (0·071), p<0·0001
6-year follow-up	0·849 (0·099), p<0·0001	0·199 (0·077), p=0·0099	0·289 (0·089), p=0·0012

Data are estimate (SE). P values were calculated with the Kenward-Roger approach, or the Satterthwaite approach if the Kenward-Roger approach was not possible. The fixed effects entered into the models were number of cigarettes smoked per day, age, time, and sex. Baseline assessment was set as reference. As random effects, intercepts for participants were added and by-subject random slopes for the effect of time. CAPE=Community Assessment of Psychic Experience. WHOQOL=WHO Quality of Life.

Table 3: **Results of linear mixed models regarding the multi-cross-sectional association between number of cigarettes per day and self-rated frequency of symptoms and quality of life corrected for sex and age**

(DSM-IV 295.1–3, 295.6, or 295.9). Table 1 and the appendix show baseline characteristics for all participants for whom data on smoking behaviour were available. At baseline, 729 (67%) of 1094 patients smoked an average of 17·5 (SD 8·8) cigarettes per day. This prevalence of daily smoking was higher than in 401 (38%) of 1047 siblings and controls (table 1). Patients also used on average more cigarettes per day compared with siblings and controls (table 1). Overall, we had follow-up data from baseline and the first timepoint about smoking for 780 (71%) patients, 795 (76%) siblings, and 446 (77%) controls. Complete data on smoking behaviour for all three timepoints were collected from 602 (55%) patients, 603 (58%) siblings, and 348 (60%) controls. At baseline, 875 patients, 920 siblings, and 551 patients provided CAPE data. CAPE baseline and follow-up data at baseline were available for 614 (70%) patients, 685 (75%) siblings, and 419 (76%) controls. Complete CAPE data for all three timepoints were available for 544 (62%) patients, 633 (69%) siblings, and 352 (64%) controls. With respect to WHOQOL data, baseline data were available for 983 patients, 951 siblings, and 521 controls. We had WHOQOL data from baseline and 3 years for 676 (69%) of 983 patients, 720 (76%) of 951 siblings, and 411 (79%) of 521 controls. Lastly, complete WHOQOL data were available for 540 (55%) patients, 632 (66%) of 951 siblings and 354 (68%) of 521 controls.

Summary scores of outcomes and exposures per group for each timepoint are shown in the appendix. In patients, mixed-effects analyses revealed that smoking was associated with more frequent self-rated positive symptoms (estimate 0·140, SE 0·024, p<0·0001), negative symptoms (estimate 0·145, 0·027, p<0·0001), and depressive symptoms (0·120, 0·028, p<0·0001) than in non-smoking (table 2). In patients, a negative association between smoking and quality of life was observed (table 2). In siblings, significant associations were found between smoking and more frequent subclinical symptoms (table 2). In control participants, we found a significant association between smoking and more frequent subclinical positive and depressive symptoms (table 2). Finally, a significantly lower level of quality of life was found in siblings who smoke (table 2) compared with non-smoking siblings.

In patients, we found positive associations between number of cigarettes smoked per day and frequency of positive, negative, and depressive symptoms, and negative associations with quality of life (table 3). In siblings and control participants, the number of cigarettes per day was also significantly associated with more frequent subclinical symptom levels and lower levels of quality of life, except for subclinical depressive symptoms in controls (table 3).

These results indicate that except for depressive symptoms, smoking, and a higher number of cigarettes per day were associated with a higher frequency of self-rated symptoms and a lower quality of life across all three groups, when adjusting for age and sex. The significant results regarding positive symptoms and emotional distress were confirmed with clinician-rated PANSS data in patients, but not for negative symptoms (appendix). Findings were not significantly affected when repeating analyses for smoking status with the addition of years of education and cannabis use as covariates in all groups and antipsychotic medication use and level of functioning covariates in patients (appendix).

Summary scores of exposure and outcome variables per group for each timepoint are described in the appendix. We found that most individuals did not change their smoking behaviour compared with their previous assessments (1238 [89%] patients; 1243 siblings [86%]; 721 control participants [91%]). However, over time, more individuals quit smoking (patients 93 [7%]; siblings 112 [8%], controls 43 [5%]) than started smoking (patients 51 [4%]; siblings 88 [6%], controls 31 [4%]). On average, over all timepoints, the number of cigarettes per day increased by 0·4 (SD 9·3) in patients, whereas siblings showed a decrease of 0·2 (SD 5·3) and controls a decrease of 0·2 (SD 4·1).

In patients, starting to smoke was associated with an increase of self-rated positive symptoms (estimate 0·137, SE 0·064, p=0·0330), negative symptoms (0·170, 0·074, p=0·0214), and depressive symptoms (0·170, 0·076, p=0·0247), but not with quality of life, compared with the

overall decrease of symptoms in those who did not change their smoking status (table 4). In unaffected siblings and controls, no significant associations were found for starting to smoke with subclinical symptom frequency or quality of life (table 4). In patients and controls, no significant results were observed for smoking cessation in relation to subclinical symptoms or quality of life (table 4). In siblings, a negative association between quitting smoking and negative symptoms was found (table 4). No other significant associations between change in smoking status and clinician-rated positive symptoms, negative symptoms, or emotional distress were found in patients (appendix). Finally, after adding all covariates to the model, only the association between starting to smoke and an increase in positive symptoms remained significant (estimate 0·161, SE 0·077, p=0·0381; appendix). In a series of sensitivity analyses, change in number of cigarettes per day in patients was also positively associated with a change in subclinical symptoms. Additional results were a negative association between number of cigarettes per day and quality of life in patients, and a positive association with depressive symptoms in siblings (table 5). Post-hoc analyses were done to explore the differences in types and dosages of antipsychotic medication between smoking and non-smoking patients (data not shown). In the subgroup of patients for whom chlorpromazine equivalents could be calculated, smokers used significantly higher antipsychotic doses than did non-smokers. Similar to the primary analyses, significant associations between smoking and symptom levels were found in the subgroups of patients who used clozapine or olanzapine and in patients who used other antipsychotics.

	Patients (n=1094)	Siblings (n=1047)	Control participants (n=579)
CAPE: frequency of positive symptoms (0–3)			
Intercept	–0·162 (0·021), p<0·0001	–0·08 (0·008), p<0·0001	–0·010 (0·008), p<0·0001
Quit smoking	–0·091 (0·049), p=0·0631	–0·019 (0·015), p=0·2153	–0·025 (0·018), p=0·1683
Started smoking	0·137 (0·064), p=0·0330	–0·001 (0·017), p=0·9771	0·038 (0·024), p=0·1174
6-year follow-up	0·085 (0·031), p=0·0061	0·075 (0·010), p<0·0001	0·077 (0·010), p<0·0001
CAPE: frequency of negative symptoms (0–3)			
Intercept	–0·105 (0·024), p<0·0001	–0·104 (0·017), p<0·0001	–0·116 (0·018), p<0·0001
Quit smoking	–0·064 (0·057), p=0·2617	–0·073 (0·035), p=0·0397	0·039 (0·044), p=0·3657
Started smoking	0·170 (0·074), p=0·0214	0·029 (0·039), p=0·4554	0·025 (0·054), p=0·6478
6-year follow-up	0·039 (0·034), p=0·0251	0·113 (0·023), p<0·0001	0·094 (0·023), p<0·0001
CAPE: frequency of depressive symptoms (0–3)			
Intercept	–0·155 (0·025), p<0·0001	–0·139 (0·016), p<0·0001	–0·146 (0·018), p<0·0001
Quit smoking	–0·021 (0·059), p=0·7247	–0·042 (0·035), p=0·2288	0·006 (0·046), p=0·8892
Started smoking	0·170 (0·076), p=0·0247	0·038 (0·039), p=0·3212	–0·006 (0·055), p=0·9125
6-year follow-up	0·101 (0·036), p=0·0052	0·1390 (0·0225), p=<0·0001	0·172 (0·024), =<0·0001
WHOQOL total score (4–20)			
Intercept	0·713 (0·085), p<0·0001	0·308 (0·073), p<0·0001	0·287 (0·084), p=0·007
Quit smoking	–0·009 (0·212), p=0·9680	0·114 (0·152), p=0·4540	–0·159 (0·217), p=0·4625
Started smoking	–0·340 (0·277), p=0·2193	–0·023 (0·170), p=0·8921	0·305 (0·256), p=0·2342
6-year follow-up	–0·689 (0·128), p<0·0001	–0·380 (0·100), p=0·0002	–0·238 (0·124), p=0·0558

Data are estimate (SE). P values were calculated with the Kenward-Roger approach, or the Satterthwaite approach if the Kenward-Roger approach was not possible. The fixed effects entered into the models were change in smoking status, age, time, and sex. Baseline assessment was set as reference. As random effects, intercepts for participants were added and by-subject random slopes for the effect of time. CAPE=Community Assessment of Psychic Experience. WHOQOL=WHO Quality of Life.

Table 4: **Results of linear mixed models regarding the association between change in smoking status and change in self-rated frequency of symptoms and quality of life corrected for sex and age**

Discussion

In line with previous studies, a much higher prevalence of smoking in patients with a psychotic disorder was seen in our observational, longitudinal cohort study compared with siblings and control participants. First, the finding that smoking is associated with more symptoms in patients as well as in siblings and healthy controls (ie, without illness-related confounders) than non-smoking, opposes the self-medication hypothesis for patients with a psychotic disorder. Second, if patients smoke to alleviate their symptoms, it would be sensible to expect that patients who quit smoking experience a worsening of symptoms or quality of life. However, patients who quit smoking compared with those in whom no change in smoking behaviour was observed did not show significant changes in symptoms. Third, starting to smoke or an increase in the number of cigarettes per day would be expected to weaken symptoms; however, we found an overall increase in self-rated, but not in clinician-rated, symptom frequency in patients who started to smoke or increased their cigarette use. After adjustment for confounders, a significant association was found for positive symptoms in the group of patients who started to smoke. As such, our long-term study does not provide support for the self-medication hypothesis as an explanation for the high prevalence of smoking in patients with psychosis.

The multi-cross-sectional findings are in line with the largest cross-sectional study and some smaller prospective studies to date. A cross-sectional study in patients with serious mental illness (n=763) found a positive association between smoking and clinician-rated symptoms and a negative association between smoking and self-rated level of functioning.[18] Our study found that smoking was associated with an increased number of self-rated symptoms, also when adjusting for important confounders such as level of functioning. These differences were present not only in patients but also in the groups without illness-related confounders. The largest prospective study to date (total n=542, with n=290 patients with psychosis or schizophrenia-related disorders), with assessment up to 10 years, found that smoking was not associated with psychotic symptoms but that the number of cigarettes covaried with depressive symptoms over time.[4] Our study also found associations between long-term changes in smoking status (eg, starting to smoke) or smoking more cigarettes per day and an increase in self-reported positive, negative, and depressive symptoms in patients with psychosis. These results remained

	Patients (n=1094)	Siblings (n=1047)	Control participants (n=579)
CAPE: frequency of positive symptoms (0–3)			
Intercept	−0·165 (0·021), p<0·0001	−0·092 (0·008), p<0·0001	−0·098 (0·008), p<0·0001
Change in number of cigarettes per day	0·005 (0·001), p=0·0015	0·001 (0·001), p=0·3855	0·002 (0·001), p=0·1278
6-year follow-up	0·082 (0·031), p=0·0083	0·075 (0·001), p<0·0001	0·076 (0·009), p<0·0001
CAPE: frequency of negative symptoms (0–3)			
Intercept	−0·108 (0·024), p<0·0001	−0·108 (0·016), p<0·0001	−0·111 (0·017), p<0·0001
Change in number of cigarettes per day	0·003 (0·001), p=0·0238	0·005 (0·002), p=0·0075	−0·005 (0·003), p=0·0830
6-year follow-up	0·042 (0·034), p=0·2115	0·111 (0·023), p<0·0001	0·092 (0·023), p<0·0001
CAPE, frequency of depressive symptoms (0–3)			
Intercept	−0·153 (0·025), p<0·0001	−0·140 (0·016), p<0·0001	−0·146 (0·018), p<0·0001
Change in number of cigarettes per day	0·004 (0·002), p=0·0048	0·004 (0·002), p=0·0210	−0·004 (0·002), p=0·1040
6-year follow-up	0·102 (0·036), p=0·0047	0·139 (0·022), p<0·0001	0·170 (0·024), p<0·0001
WHOQOL total score (4–20)			
Intercept	0·716 (0·083), p<0·0001	0·308 (0·071), p<0·0001	0·276 (0·083), p=0·0009
Change in number of cigarettes per day	−0·002 (0·006), p=0·0002	−0·013 (0·008), p=0·1038	0·024 (0·013), p=0·0621
6-year follow-up	−0·704 (0·126), p<0·0001	−0·378 (0·100), p=0·0002	−0·224 (0·124), p=0·0725

Data are estimate (SE). P values were calculated with the Kenward-Roger approach, or the Satterthwaite approach if the Kenward-Roger approach was not possible. The fixed effects entered into the models were change in number of cigarettes per day, age, time, and sex. Baseline assessment was set as reference. As random effects, intercepts for participants were added and by-subject random slopes for the effect of time. CAPE=Community Assessment of Psychic Experience. WHOQOL=WHO Quality of Life.

Table 5: **Results of linear mixed models regarding change in number of cigarettes per day and change in self-rated frequency of symptoms and quality of life corrected for sex and age**

significant for positive symptoms after controlling for multiple confounders. No significant differences were observed in clinician-rated symptoms with respect to change in smoking behaviour. Since the self-medication hypothesis focuses on the subjective experience of patients, we believe that the self-rated results are important to address our research questions. These self-rated findings do not support the self-medication hypothesis, according to which one would expect a decrease of symptoms. The mechanism that explains our findings is, however, unclear. There could be reverse causation (eg, patients with an increase of symptoms might also start to smoke or smoke more frequently). Another explanation is a difference in short-term and long-term effects. Some patients report that they smoke because it helps them cope with stress and for relaxation, or because of physiological effects or for stimulation.[19] The long-term effects, however, remain unclear. The amount of biological evidence about nicotine and its binding to and subsequent desensitisation of the nicotinic acetylcholine receptor is growing.[20] However, to the best of our knowledge, this association has not yet been studied in relation to a change in biochemistry of the brain or long-term clinical outcomes. The harm from toxic compounds within cigarettes is known to be extensive. Chronic exposure affects brain morphology and perfusion[21] and possibly brain functioning or severity of psychopathology via various pathways (eg, oxidative stress and atherosclerosis). Furthermore, after correcting for various confounders, this study did not validate the findings of a meta-analysis about smoking cessation.[22] The meta-analysis showed a positive effect of smoking cessation on quality of life and a reduction of symptom levels. Important differences are the smaller number of participants who quit smoking in our study than in the meta-analysis and that participants in our study were not involved in a study that assessed a smoking cessation programme.

The main strengths of our study are the large sample size, the wide range of clinical measures with self-rated and clinician-rated measurements, the presence of two comparison groups (one of which controlled for genetic and environmental factors), the prospective long-term nature of the study, and that the analyses included several important covariates to decrease the risk of residual confounding. Our study has some limitations. First, because of the observational nature of the study, reverse causation and residual confounding cannot be completely ruled out. Second, we had insufficient information from participants about continuous exposure or short-term effects of smoking. Observation points within the GROUP have a 3-year interval and individuals were interviewed about their smoking behaviour regarding daily smoking within a month during the past 12 months before the assessment. Therefore, we could observe trends but not acute effects of smoking on symptoms and quality of life. Third, we could not present analyses using medication dose because these data were often missing. However, post-hoc analyses suggested that insufficient treatment of smokers, due to increased metabolisation of antipsychotics, is unlikely to explain the higher frequency of symptoms in smokers. Moreover, the type of antipsychotic that was used could not explain the association between smoking and symptom levels because similar associations were found in patients who used clozapine and olanzapine (eg, antipsychotics which metabolisation is mostly affected by smoking). Fourth, as with any follow-up study,[23] this cohort study encountered loss to follow-up, which is especially an issue in patients with a severe mental illness and a reduced level of functioning. We assumed that missingness was at random and we included several covariates (eg, level of functioning) in the mixed-model analyses to make this assumption tenable and minimise the influence of missing data. Lastly, patients in the GROUP study represent a relatively high functioning cohort with a probably lower prevalence of smoking, lower level of symptoms, and higher quality of life than the average patient with psychosis. This limits the generalisability of our findings.

In summary, our findings do not support the self-medication hypothesis with respect to smoking and long-term results of symptomatology or quality of life in patients with a psychotic disorder. Although the observed differences are small, these differences are clinically relevant since the associations are in the opposite direction

of what is expected when the self-medication hypothesis would be correct. Another explanation for the high prevalence of smoking in patients with psychosis is the shared-vulnerability hypothesis.[24] This hypothesis postulates that patients with psychosis frequently smoke because of shared genetic or environmental factors between smoking and psychosis[25] that predispose them to addiction and schizophrenia. Furthermore, observational studies, some using Mendelian randomisation,[26] have identified smoking as a causal risk factor for developing psychosis.[27,28] Ultimately, the prevalence of smoking in patients with psychosis should be decreased to improve their health and reverse the dramatic reduction of life expectancy that is caused by cigarette smoking.[29] Our long-term results, combined with previous studies, underline that smoking provides little or no benefit to patients through the observation of more frequent self-rated symptoms and lower quality of life in smokers than in non-smokers from all groups and an overall disadvantage in terms of symptoms of smoking initiation or increasing the number of cigarettes per day in patients. Many clinicians still hold negative attitudes and misconceptions.[30] A frequently mentioned negative attitude was "Quitting smoking would make other mental health symptoms worse".[31] This problem hinders the implementation of treatment for nicotine addiction in this group. Our study provides new long-term evidence that argues against this statement and hopefully this will encourage clinicians to initiate smoking cessation treatment in their patients.

Contributors

JV contributed to the literature search, figures, data analysis, data interpretation, and writing. FS contributed to the data collection, figures, data analysis, data interpretation, and writing. MB contributed to figures, data analysis, data interpretation, and writing. MvT contributed to the data interpretation and writing. WvdB contributed to the figures, data analysis, data interpretation, and writing. LdH contributed to the study design, data collection, figures, data analysis, data interpretation, and writing. The GROUP investigators contributed to the study design, data collection, and writing.

Declaration of interests

WvdB received speakers' fees from Lundbeck, Indivior, Eli Lilly, and Pfizer and he is a consultant to Indivior, Mundipharma, Novartis, Bioproject, D&A Pharmaceuticals, and Opiant Pharmaceuticals. All other authors declare no competing interests.

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References

1 de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005; **76:** 135–57.

2 Manzella F, Maloney SE, Taylor GT. Smoking in schizophrenic patients: a critique of the self-medication hypothesis. *World J Psychiatry* 2015; **5:** 35–46.

3 Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv Rev Psychiatry* 1997; **4:** 231–44.

4 Kotov R, Guey LT, Bromet EJ, Schwartz JE. Smoking in schizophrenia: diagnostic specificity, symptom correlates, and illness severity. *Schizophr Bull* 2010; **36:** 173–81.

5 Levander S, Eberhard J, Lindstrom E. Nicotine use and its correlates in patients with psychosis. *Acta Psychiatr Scand Suppl* 2007; 27–32.

6 Cerimele JM, Katon WJ. Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. *Gen Hosp Psychiatry* 2013; **35:** 16–22.

7 Korver N, Quee PJ, Boos HB, Simons CJ, de Haan L. Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *Int J Methods Psychiatr Res* 2012; **21:** 205–21.

8 Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington: American Psychiatric Publisher, 2000.

9 WHO. Composite International Diagnostic Interview (CIDI): a) CIDI-interview (version 1.0), b) CIDI-user manual, c) CIDI-training manual, d) CIDI-computer programs. Geneva: World Health Organization, 1990.

10 Cottler LB, Robins LN, Helzer JE. The reliability of the CIDI-SAM: a comprehensive substance abuse interview. *Br J Addict* 1989; **84:** 801–14.

11 Mossaheb N, Becker J, Schaefer MR, et al. The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. *Schizophr Res* 2012; **141:** 210–14.

12 Power M, Kuyken W, Orley J, et al. The World Health Organization quality of life assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med* 1998; **46:** 1569–85.

13 Trompenaars FJ, Masthoff ED, Van Heck GL, Hodiamont PP, De Vries J. Content validity, construct validity, and reliability of the WHOQOL-Bref in a population of Dutch adult psychiatric outpatients. *Quality Life Res* 2005; **14:** 151–60.

14 Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13:** 261–76.

15 van der Gaag M, Hoffman T, Remijsen M, et al. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. *Schizophr Res* 2006; **85:** 280–87.

16 Vermeulen J, Schirmbeck F, Blankers M, et al. Association between smoking behavior and cognitive functioning in patients with psychosis, siblings, and healthy control subjects: results from a prospective 6-year follow-up study. *Am J Psychiatry* 2018; **175:** 1121–28.

17 Luke SG. Evaluating significance in linear mixed-effects models in R. *Behav Res Methods* 2017;**49:** 1494–502.

18 Depp CA, Bowie CR, Mausbach BT, et al. Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta Psychiatr Scand* 2015; **131:** 333–41.

19 Clark V, Baker A, Lewin T, et al. Self-reported reasons for smoking: predicting abstinence and implications for smoking cessation treatments among those with a psychotic disorder. *J Dual Diagn* 2017; **13:** 6–14.

20 Brody AL, Mandelkern MA, London ED, et al. Cigarette smoking saturates brain alpha(4)beta(2) nicotinic acetylcholine receptors. *Arch Gen Psychiatry* 2006; **63:** 907–15.

21 Durazzo TC, Meyerhoff DJ, Nixon SJ. Chronic cigarette smoking: implications for neurocognition and brain neurobiology. *Int J Environ Res Public Health* 2010; **7:** 3760–91.

22 Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014; **348:** g1151.

23 Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol* 2004; **19:** 751–60.

24 Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 2001; **50:** 71–83.

25 Gage SH, Munafo MR. Rethinking the association between smoking and schizophrenia. *Lancet Psychiatry* 2015; **2:** 118–19.

26 Wootton RE, Richmond RC, Stuijfzand BG, et al. Causal effects of lifetime smoking on risk for depression and schizophrenia: evidence from a Mendelian randomisation study. *bioRxiv* 2018; published online Aug 1. DOI:10.1101/381301 (preprint).

27 Mustonen A, Ahokas T, Nordstrom T, et al. Smokin' hot: adolescent smoking and the risk of psychosis. *Acta Psychiatr Scand* 2018; **138:** 5–14.

28 Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* 2015; **2:** 718–25.

29 Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry* 2015; **72:** 1–10.

30 Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs* 2017; **31:** 471–81.

31 Sheals K, Tombor I, McNeill A, Shahab L. A mixed-method systematic review and meta-analysis of mental health professionals' attitudes toward smoking and smoking cessation among people with mental illnesses. *Addiction* 2016; **111:** 1536–53.