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Association between tobacco use and symptomatology in individuals at ultra-high risk to develop a psychosis: A longitudinal study

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ABSTRACT

Background: The high prevalence rates and impact of tobacco smoking in individuals with a psychotic disorder have become an increasing interest. Little is known about tobacco smoking in individuals at ultra-high risk of psychosis (UHR).

Methods: We studied 345 UHR individuals of the high-risk study of the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI). Smoking status and the number of cigarettes per day were assessed at multiple moments using the CIDI. Symptom severity at each time point was assessed using CAARMS. Linear mixed-effects analyses were conducted to examine the multi-cross-sectional and prospective associations between (change in) smoking behaviour and symptomatology.

Findings: At baseline, 175 individuals (53%) smoked tobacco with an average of 12.4 (SD = 9.0) cigarettes per day. Smokers did not significantly differ in symptom severity from non-smokers on general, positive, negative, emotional, cognitive, behavioural, or motor symptoms across time. However, associations were found between the number of cigarettes and the severity of general psychopathology (estimate 0.349, SE 0.146, $p = 0.017$). Change in the number of cigarettes had no significant effect on change in general symptom severity (estimate 0.330, SE 0.285, $p = 0.248$).

Interpretation: Smoking prevalence in UHR individuals is high. Cigarette consumption was associated with higher levels of general symptoms. However, we observed no association between change in number of cigarettes and symptom severity. Given the fact that smoking is associated with poorer health and worse outcomes in people with psychosis, the clinical high-risk phase offers a window of opportunity for prevention and cessation interventions.

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1. Introduction

Tobacco use is the leading cause of preventable diseases, disabilities, and death in Western countries. According to the World Health Organization (World Health Organization, 2017; Kotov et al., Jan 2010) tobacco use is responsible for killing more than seven million people each year globally, and one in ten deaths around the world is caused by tobacco use. In the past decades, the prevalence of smoking has been decreased in daily life in Western countries: the overall global rate of current smoking aged over 15 years, declined from 23.5% in 2007 to 20.7% in 2015 (Organization WH, 2017). However, this is not the case for individuals with a psychiatric condition, and especially not in psychosis: the smoking prevalence remains extremely high, with rates varying from 57.0% in first-episode psychosis (Gurillo et al., 2015) and 61.6% in schizophrenia (Zeng et al., Jun 6 2020). Smoking has been associated with higher levels of symptom severity, especially positive (Vermeulen et al., 2019; Oluwoye et al., Feb 2019; Huang et al., 2019), negative (Oluwoye et al., Feb 2019) and depressive symptoms (Kotov et al., Jan 2010) in subjects with a psychotic disorder.

To further understand the association between smoking and psychotic symptoms, it is essential to evaluate this link in different stages of the illness. Individuals who are susceptible to develop a psychosis, but did not yet cross the threshold for a psychotic disorder are of great interest, since the onset of smoking often predates the onset of psychosis. A recent literature review (Gogos et al., 2019) evaluated nicotine consumption during the clinical high risk phase of psychosis. The smoking prevalence in individuals at risk for psychosis, also referred to as ultra-high risk (UHR), was higher compared to healthy controls, with rates between 16.6 and 46% in UHR. In addition, UHR subjects were almost five times as likely to be heavy smokers compared to unaffected subjects (Ward et al., Oct 2019). Limited evidence was found to suggest that tobacco use in UHR was associated with an increased risk to transition to psychosis (Gogos et al., 2019; Ward et al., Oct 2019). The authors (Gogos et al., 2019) attempted to evaluate whether UHR subjects who smoked differed from non-smoking UHR subjects regarding cognition and clinical symptoms. Two studies examined cognitive performance (Gupta and Mittal, 2014; Cadenhead, 2011) in UHR individuals and concluded that smoking UHR individuals outperformed their non-smoking peers. With respect to the associations with clinical symptoms, the authors concluded that data were insufficient and the need for prospective studies was highlighted.

This present study aimed to address this issue in a prospective study of a large sample of UHR subjects. We first tested the hypothesis that tobacco use would be multi-cross-sectionally associated with higher severity of symptoms (general, positive, negative, emotional, cognitive, behavioural, and motor change symptoms). Based on previous studies, we expected that the severity of symptoms would be positively associated with the number of cigarettes smoked per day (Vermeulen et al., 2019). Second, we investigated the relationship between change in smoking behaviour and change in symptoms over time. Due to previous conflicting results in individuals with a psychiatric condition (Taylor et al., Feb 13 2014) and individuals with psychosis (Kotov et al., Jan 2010; Vermeulen et al., 2019), we expected that change in smoking behaviour would not be associated with diminished nor increased symptom severity.

2. Methods

2.1. Study design

Participants were part of the high-risk study of the European network of national schizophrenia networks studying gene-environment Interactions (EU-GEI) cohort (Schizophrenia ENoNNsG-EIi et al., Jul 2014; Menghini-Muller et al., Jun 2019). The overall aim of EU-GEI is the identification of clinical, genetic, and environmental interactions in the development, severity, and course of psychotic disorders in participants and their families. EU-GEI is a multicentre, naturalistic prospective study conducted between May 1, 2010, to April 30, 2015, and consisted of a baseline measurement and three follow-up time points (at six months, one year, and two years).

2.2. Participants

In our study, 345 UHR individuals were included. Participants were aged between 15 and 45 years and were recruited from 11 early detection centres (Amsterdam, Den Haag, Vienna, Basel, Cologne, Melbourne, Copenhagen, Paris, Barcelona, Sao Paulo, and London). Participants were included in the study if they met at least one of three UHR criteria as defined by the *Comprehensive Assessment of At-risk Mental State (CAARMS)* (Yung et al., 2005): 1. The Vulnerability Group: a first-degree relative with a psychotic disorder or diagnosed with schizotypal personality disorder in combination with a significant drop in functioning during at least 1 month in the previous year, 2. The Attenuated Psychotic Symptoms (APS) Group: the presence of subthreshold positive psychotic symptoms for at least 1 month during the past year, or 3. The Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group: an episode of frank psychotic symptoms that lasted no longer than 1 week, which abated spontaneously. Exclusion criteria were: prior experience of a psychotic episode of more than one week, as determined by the CAARMS (Yung et al., 2005), or an intelligence quotient (IQ) below 60. For the current study, UHR subjects were included if they provided data on smoking at baseline and psychopathology (CAARMS) at least at one assessment. All participants provided informed, written consent following a full explanation of the study. Relevant research ethics committees in each of the study sites provided ethical approval.

2.3. Assessment instruments

Detailed information about the use of tobacco during the past year was assessed using the *Composite International Diagnostic Interview (CIDI)* which has been found to be reliable in a cross-cultural trial (Cottler et al., 1989). Smokers were defined as people who smoked daily for at least one month over the past 12 months. Data on the use of cigars, chewing and snuffing tobacco or on the use of electronic nicotine delivery systems were not available in the current study. Participants were asked how many cigarettes they smoked per day in the time frame they smoked the most during the past 12 months. Symptom severity was assessed using the CAARMS (Yung et al., 2005), a semi-structured interview designed to assess the at-risk mental states for psychosis. The CAARMS provides ordinal scores for the severity of psychotic symptoms as well as other dimensions of psychopathology (Morrison et al., 2012). In our study, outcome variables were based on the seven symptom domains of the CAARMS, namely: positive symptoms (items: unusual thought content, non-bizarre ideas, perceptual abnormalities, disorganized speech); negative symptoms (alogia, avolition/apathy, anhedonia); motor/physical change (subjective complaints of impaired motor functioning, observed change in motor functioning); behavioural change (social isolation, impaired role function, disorganizing/odd/stigmatizing behaviour, aggression/dangerous behaviour); cognitive change attention/concentration (subjective experience, observed cognitive change); emotional disturbance (subjective emotional disturbance, observed blunted affect, observed inappropriate affect) and general psychopathology (mania, depression, suicidality/self-harm, mood swings/lability, anxiety, obsessive-compulsive symptoms, dissociative symptoms and subjective impaired tolerance to normal stress). The composite score for our outcome variables (7 subscales) was computed by summing intensity * frequency score (both scored on a Likert scale 0 to 6) of the corresponding items, as per previous research (Morrison et al., 2012; Lim et al., 2015). See supplement 1 and 2 for detailed information about available data for smoking status and CAARMS subscales.

2.4. Covariates

All participants provided information on sociodemographic features, such as their gender, age, education, and current employment. Social functioning was scored using the *Global Assessment of Functioning* (GAF, range 0–100) (Goldman et al., 1992). The *Cannabis Experience Questionnaire (CEQ)* was administered to assess information regarding the use of cannabis. Participants answered either "yes" or "no" in response to being asked, "Do you currently use marijuana?" Those who reported "yes" to cannabis use were classified as "cannabis users." *The Childhood Trauma Questionnaire (CTQ)* serves as a valid retrospective assessment of childhood trauma (Liebschutz et al., Jun 2018). This 25-item self-report questionnaire assesses traumatic events before the age of 17 and was used to report information on 5 subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect), as well as a total score of all 5 subscales (range 0-6). Age, gender, socioeconomic status (including education, current employment, and GAF scores), childhood trauma, and cannabis use were a-priori selected as covariates since these variables were found to be associated with both smoking and symptom severity (Kotov et al., Jan 2010; Vermeulen et al., 2019; Kraan et al., 2018).

2.5. Statistical analyses

Statistical analyses were performed in IBM SPSS Statistics version 26 (Chicago, Illinois, USA). Complete case analysis at baseline revealed missing data on several items (supplement 4) that were missing at random. Therefore, multiple imputation was applied which is a generally accepted solution to deal with incomplete data (van Buuren et al., 1999; Sterne et al., Jun 29 2009; van Buuren, 2012). Multiple imputation was applied at baseline for socioeconomic status (including education, current employment, and GAF scores), CAARMS individual items, and information about the use of cannabis (current and lifetime use). Linear mixed models were used to assess associations between smoking and symptoms severity across different assessment times over a period of two years (multi-cross-sectional). This method allowed us to deal with the non-independence of the data due to repeated assessment. Every subject with at least one assessment was included and models were fitted using maximum likelihood estimation (Harrison et al., 2018; Seltman, 2012). We compared smoking and non-smoking participants on baseline characteristics with independent *t*-tests, Whitney *U* tests, and X^2 for normal distributed, non-normal distributed and categorical data, respectively. Visual inspection of residual plots of all seven CAARMS subscales revealed no deviations from normality. Continuous variables were centered (Bolger and Laurenceau, 2013) to improve model performance and interpretability (Harrison et al., 2018).

To answer the first research question, we set symptom severity as measured with seven subscales of the CAARMS as the outcome variables. In the first model, smoking status (yes/no), time, age, and gender were entered as fixed effects. If models showed significant results, the following a priori selected covariates were added en bloc: GAF, education, work, cannabis, and trauma scores. In all models, subjects were added as random intercept and time was added as random slope. To investigate a dose-response relationship, we ran a second set of linear mixed effect models replacing smoking status by the number of cigarettes.

To answer the second research question, three groups were identified between assessments (1 year compared to baseline, 2 years compared to 1 year): participants who did not change their smoking behaviour, participants who were able to quit smoking, and participants who started smoking cigarettes. In addition, change scores regarding the number of cigarettes smoked were calculated. Furthermore, change scores on outcome variables were calculated. We applied two sets of linear mixed models with similar covariates as fixed, and random effects as mentioned earlier. *P*-values were calculated by the Satterthwaite method which has been evaluated in REML-fitted models and produced the most acceptable type I error rates in mixed-effects models (Luke, Aug 2017).

3. Results

3.1. Sample characteristics

345 UHR individuals participated in the EU-GEI study. Sociodemographic features and clinical characteristics are presented in Table 1. For the current analyses, only UHR individuals with data on smoking and at least one assessment with the CAARMS were included ($n = 330$). As we were interested in associations over an approximately two year period, assessments dates with extreme deviation (>1000 days from baseline) were excluded ($n = 23$) in the mixed model analysis. Assessments at six months were scarce in most inclusion sites, as this time point was introduced later in the study, and not due to any patient-specific reasons. Both CAARMS data (positive symptoms) and smoking status data were available for 41 (12.5%) individuals at six months, compared to 169 (51.5%) and 123 (39.4%) at one- and two-year follow-up, respectively. See supplement 3 for other subscales.

3.2. Baseline comparisons

In total, 175 individuals (53%) smoked at baseline with an average of 12.4 (SD = 9.0) cigarettes per day. Baseline comparisons showed that smokers were significantly older than non-smokers and reported more current or lifetime cannabis use. They also had lower GAF scores and had experienced significantly more physical abuse during childhood. Between-group comparisons (smokers vs. non-smokers) showed no significant differences at baseline on any of the CAARMS subscales. In our sample, detailed information about medication use (i.e. dose-equivalents and compliance) was incomplete. Overall, 35% of smoking individuals used psychotropic medication, compared to 40% of non-smoking individuals. There were no significant between-group differences in transition rate between smoking UHR individuals and non-smoking individuals (see Table 1).

3.3. Association between smoking and symptom severity

Mixed model analyses showed no significant multi-cross-sectional differences between UHR individuals who did and did not smoke on any outcome variable (supplement 5).

3.4. Association between the number of cigarettes smoked per day and symptom severity

A positive association was found between the number of cigarettes and the severity of general psychopathology (estimate 0.376, SE 0.146, $p = 0.010$). This association remained after correcting for confounding variables (estimate 0.349, SE 0.146, $p = 0.017$), as shown in Table 2.

Besides general symptoms, a positive association was also found between the number of cigarettes smoked per day and behavioural change symptoms (estimate 0.219, SE 0.099, $p = 0.026$). However, significance was lost after correction for confounding variables (supplement 6). We found no significant association between the number of cigarettes smoked per day and symptom severity on the other five CAARMS subscales (positive, negative, emotional, cognitive, or motor change symptoms) (supplement 6).

3.5. Association between change in number of cigarettes smoked and change in symptom severity

Post hoc exploratory analyses did not show a significant association between change in the number of cigarettes smoked and change in the severity of general psychopathology (estimate 0.330, SE 0.285, $p = 0.248$) (supplement 7).

Table 1
Baseline characteristics of smoking and non-smoking UHR individuals.

	Smoking N = 175 (53%)	Non-smoking N = 155 (47%)	Value	p-Value*
Gender				
Male	100 (57%)	77 (50%)	X = 1842	0,186
Female	75 (43%)	78 (50%)		
Age	23,1 (5,0)	21,7 (4,8)	Z = −2813	0,005†
GAF	53,8 (11,3)	57,6 (13,4)	T = 2818	0,005
Education in years	14,19 (3,1)	14,38 (3,1)	T = 0,556	0,579
Current employment				
No paid work	82 (47%)	60 (39%)	X = 2226	0,136
Student/paid work	93 (53%)	95 (61%)		
Cannabis				
Ever used cannabis	164 (94%)	75 (48%)	X = 84,559	<0,001
Current use cannabis	68 (39%)	17 (11%)	X = 33.433	<0,001
Trauma				
Emotional abuse	2,5 (1,0)	2,4 (1,1)	Z = −0,891	0,373†
Physical abuse	1,6 (0,8)	1,4 (0,7)	Z = −2214	0,027†
Sexual abuse	1,5 (0,9)	1,4 (0,8)	Z = −1833	0,067†
Emotional neglect	2,7 (1,0)	2,7 (1,0)	Z = −0,900	0,368†
Physical neglect	1,7 (0,7)	1,7 (0,6)	Z = −0,355	0,722†
Total trauma score	9,5 (3,1)	9,9 (3,2)	Z = 1393	0,164
CAARMS				
General psychopathology	58,9 (29,2)	54,7 (28,9)	Z = −1077	0,281†
Positive symptoms	37,3 (19,5)	36,8 (19,9)	T = −0,228	0,820
Negative symptoms	30,7 (18,5)	28,0 (18,4)	Z = −1511	0,188†
Emotional symptoms	13,4 (11,7)	12,1 (10,8)	Z = −0,721	0,471†
Cognitive symptoms	9,9 (6,5)	9,9 (5,7)	Z = −0,223	0,824†
Behavioural change symptoms	33,3 (19,4)	29,2 (19,7)	T = −1890	0,060
Motor change symptoms	7,5 (10,1)	6,9 (9,0)	Z = −0,188	0,851†
Medication				
Current use of antipsychotics	15 (10%)	11 (9%)	X = 0,125	p = 0,724
Current use of antidepressants	40 (27%)	40 (32%)	X = 0,889	p = 0,346
Current use of anxiolytics	14 (9%)	12 (10%)	X = 0,004	p = 0,951
Transition to psychosis	175	155		
Yes	30 (17%)	32 (21%)	X = 0,661	p = 0,416
No	145 (83%)	123 (79%)		

Data are in N (%) or mean (SD). GAF: Global Assessment of Functioning. CAARMS: Comprehensive Assessment of At-risk Mental State. Imputated data: GAF scores, education, current employment, cannabis, trauma scores and individual CAARMS items. Two sides p-values were computed by an independent t-test, Mann-Whitney U test† or a X^2 test.

Table 2
Results of liner mixed model regarding the multi-cross sectional association between amount of cigarettes and general psychopathology in UHR individuals.

CAARMS: general psychopathology			
	Estimate	SE	p
Intercept	28,960	6234	<0,001
Amount of cigarettes	0,349	0,146	0,017
Time	-6924	0,825	0,000

CAARMS: Comprehensive Assessment of At-risk Mental State. The following fixed effects were added to the model: age + gender + time, GAF scores, education, work, cannabis and trauma scores. Subject was added as random intercept and time was added as random slope.

4. Discussion

This prospective, longitudinal study showed that smoking prevalence among people at UHR for psychosis was high (53%). No associations were found between smoking status and symptom severity in UHR individuals, nor between smoking status and transition rate. However, we observed a dose-response relationship between the number of cigarettes smoked per day and higher levels of general symptom severity in UHR individuals. A smoking prevalence of 53% in the current UHR sample is substantially higher compared with the general population, but somewhat lower compared to subjects with psychosis (Chapman et al., Mar 2009; Parikh et al., 2016; Volkow, 2009). A systematic review focussing on cardiometabolic risk factors in UHR individuals (Carney et al., 2016) found an overall smoking prevalence of 33%. However, many of the studies in this systematic review excluded individuals with comorbid substance abuse. This might suggest that the overall smoking prevalence in the latter study was underestimated because tobacco smoking and comorbid substance abuse frequently co-occur. Our results are in line with two other smaller studies (Gupta and Mittal, 2014; Egerton et al., 2014) (N = 35 and N = 75), which found a smoking prevalence of 46 and 61%, respectively.

In contrast with our first hypothesis, we found no significant association between smoking status (yes or no) and symptom severity in UHR individuals. To the best of our knowledge, we could not find previous studies that examined the association between smoking and symptom severity in UHR. Our findings are at odds with the evidence in individuals who already crossed the diagnostic border of a psychotic disorder, in whom a positive association between smoking status and higher symptom levels of positive, negative, and depressive symptoms was reported (Vermeulen et al., 2019; Oluwoye et al., 2019). Current findings could be viewed as partially in line with results from a recent meta-analysis (Huang et al., 2019) which found more positive symptoms in smoking subjects with psychosis, but no effect on negative, depressive, and anxiety symptoms.

Several, non-mutually exclusive hypotheses exist trying to explain the relationship between tobacco smoking and symptom severity in individuals with psychiatric illnesses, such as causal relationship (Kendler et al., 2015; Mustonen et al., 2018; Wootton et al., 2019), a shared vulnerability (Gage and Munafo, 2015; Hu et al., 2018; Liu et al., 2019), dysfunctional coping (Moon et al., 2014), or self-medication (Kumari and Postma, 2005; Dome et al., 2010). In our study, the smoking prevalence of UHR individuals is 3-fold higher than in healthy controls (Fusar-Poli et al., 2017). Multiple studies (Gurillo et al., 2015; Kendler et al., 2015; Mustonen et al., 2018; Wootton et al., 2019) found that smoking is a causal risk factor for developing psychosis. It is hypothesized that nicotine disrupts neurotransmitters and that toxic compounds in cigarettes may induce immune upregulation, which might contribute to the onset of mental illness. With regard to this hypothesis, no conclusions can be drawn as the current study was not designed to study whether smoking has a causal effect on psychosis.

We found no association between smoking and transition, which is in line with results from Ward et al., who evaluated the role of nicotine in the development of psychosis (Ward et al., 2019). The high prevalence of smoking in the early at-risk mental state may support the hypothesis that shared genetic and environmental risk factors account for the co-existence of smoking and (subclinical) psychotic symptoms. Liu et al. (Liu et al., 2019) found evidence for a genetic correlation between schizophrenia and smoking, with overlapping genome-wide associated single nucleotide polymorphisms in the gene cluster coding for nicotine

receptor subunits. Second, smoking and schizophrenia share important environmental risk factors such as socioeconomic status, traumatic events and drug abuse (Kendler et al., 2015; Fusar-Poli et al., 2020; Do and Maes, 2017) that may account for a part of the explained variance in the link between smoking and psychosis. Therefore, individuals with a high risk for psychosis might also be genetically and environmentally more prone to start smoking compared to the general population. This explanation is also plausible for the association between depressive symptoms or disorder and smoking. One study (Edwards et al., 2011) evaluating same-sex twins from the general population found that both genetic and environmental influences contribute to the co-occurrence of depression and smoking in females.

Although we found no associations with smoking status, we found an association between the number of cigarettes smoked per day and the severity of general symptoms. As mentioned above, the majority of items included in the general symptoms subscale measures affective symptoms. Depressive and anxiety disorders are the main reasons why UHR individuals seek help as they cause substantial distress (Falkenberg et al., 2015). In addition to possible shared underlying vulnerabilities, the high prevalence of smoking and associations with more affective symptoms might support an alternative hypothesis of dysfunctional coping. Higher levels of depression and anxiety in UHR individuals have been found associated with maladaptive coping patterns (Lee et al., 2011). According to a systematic review (Mian et al., 2018), UHR individuals use indeed more maladaptive coping, negative, avoidant and fewer adaptive coping strategies than healthy controls. In this line, smoking may represent a maladaptive coping strategy (Clark et al., 2017), in trying to cope with the presence of anxiety and or depressive symptoms instead of applying other (more healthy) behavioural strategies to alleviate these symptoms. One study in UHR found indeed that stressful life events were associated with an increased risk to smoke (Ward et al., Oct 2019). However, maladaptive avoidant coping strategies (including smoking) may also lead to increased general symptom severity (Lee et al., Feb 2011).

With respect to the self-medication hypothesis (Kumari and Postma, 2005; Dome et al., 2010), stimulation of nicotinic-acetylcholine receptors triggers a release of a variety of neurotransmitters which might alleviate psychiatric symptoms. In our study, the association with more severe general symptoms and the lack of an association between change in the number of cigarettes and symptom severity challenges the self-medication hypothesis. This is in line with several recent studies in psychosis. For example, a multicentre, longitudinal cohort study (Vermeulen et al., 2019) found that smoking cessation was not associated with changes in symptoms while starting smoking was associated with an increase in positive symptoms. Interestingly, smoking might also be relevant for other symptom domains such as cognitive functioning. Two studies (Gupta and Mittal, 2014; Cadenhead, 2011) in UHR individuals found that nicotine use was associated with improved functioning on certain cognitive domains and the authors hypothesized that influence on nicotinic-acetylcholine receptors could lead to enhanced cognitive function, at least over the short term (also known as the gating deficit hypothesis (Brockhaus-Dumke et al., 2008; Turetsky et al., 2012)).

4.1. Strengths and limitations

The main strengths of the current study are the prospective, longitudinal design and the inclusion of a large sample of UHR participants. Furthermore, this study was conducted in a wide range of settings across the world. This maximises its generalisability and importance for public health interventions. However, the current study has several limitations that should be acknowledged. First, due to the observational design of our study, reverse causation and residual confounding cannot be ruled out. A second limitation is the lack of information regarding the initiation of tobacco use prior to symptoms. A meta-analysis (Myles et al., 2012) found that tobacco use begins on average five years before the onset of psychosis. A third limitation of this study is the lack of a control group. Fourth, assessments at six months were scarce (12.5%) in most centres due to differences in study design procedures. Nevertheless, in evaluating change scores over time we compared symptomatology and the number of cigarettes based on a one-year scale (2 years compared to 1 year, 1 year compared to baseline). However, also a substantial number of participants was lost to follow-up (49% and 61%) at one and two years, respectively. As a consequence, the limited sample size may have underpowered the change analysis. Fifth, we were not able to present an analysis using medication doses because detailed data was incomplete. Therefore, the use of medication was not included as a confounding variable. However, sensitivity analyses were done in a subsample of UHR ($N = 272$) individuals which revealed the same results as the primary analyses. Finally, the fact that only individuals who were seeking help were included indicates that a selection bias could be present and that these findings should be generalised with caution.

4.2. Clinical implications

Our findings concerning a high prevalence of smoking, an association between smoking severity and severity of general symptoms and the lack of any beneficial effects support the goal of prevention and stopping smoking in subjects at UHR. A recent meta-analysis and randomised controlled trial (Gilbody et al., 2019) showed that subjects with severe mental illness are a harder-to-treat population (Zeng et al., 2020). This means that they need more quit attempts and more support. Since UHR individuals suffer less from symptoms than individuals with a first psychotic episode, this phase might be a window of opportunity to provide smoking cessation support. Early intervention smoking cessation programs should therefore be offered when UHR individuals present to psychiatric services. The knowledge that number of cigarettes smoked was associated with more severe general symptomatology and that anxiety, depression, and stress can decrease after smoking cessation (Taylor et al., 2014), will hopefully boost motivation to decrease or stop smoking.

Contributors

All authors are responsible for reported research and all authors have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and they have all approved the manuscript as submitted.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.08.006.

References

Bolger, N., Laurenceau, J.-P., 2013. Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research. Guilford Press, New York, NY, US.

Brockhaus-Dumke, A., Schultze-Lutter, F., Mueller, R., et al., 2008. Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients. Biol. Psychiatry 64 (5), 376–384.

van Buuren, S., 2012. Flexible Imputation of Missing Data. Taylor & Francis.

van Buuren, S., Boshuizen, H.C., Knook, D.L., 1999. Multiple imputation of missing blood pressure covariates in survival analysis. Stat. Med. 18 (6), 681–694.

Cadenhead, K.S., 2011. Startle reactivity and prepulse inhibition in prodromal and early psychosis: effects of age, antipsychotics, tobacco and cannabis in a vulnerable population. Psychiatry Res. 188 (2), 208–216.

Carney, R., Cotter, J., Bradshaw, T., Firth, J., Yung, A.R., Feb 2016. Cardiometabolic risk factors in young people at ultra-high risk for psychosis: a systematic review and meta-analysis. Schizophr. Res. 170 (2–3), 290–300.

Chapman, S., Ragg, M., McGeechan, K., Mar 2009. Citation bias in reported smoking prevalence in people with schizophrenia. Aust. N. Z. J. Psychiatry 43 (3), 277–282.

Clark, V., Baker, A., Lewin, T., et al., 2017. Self-reported reasons for smoking: predicting abstinence and implications for smoking cessation treatments among those with a psychotic disorder. J. Dual Diagn. 13 (1), 6–14.

Cottler, L.B., Robins, L.N., Helzer, J.E., Jul 1989. The reliability of the CIDI-SAM: a comprehensive substance abuse interview. Br. J. Addict. 84 (7), 801–814.

Do, E.K., Maes, H.H., 2017. Genotype x environment interaction in smoking behaviors: a systematic review. Nicotine Tob. Res. 19 (4), 387–400.

Dome, P., Lazary, J., Kalapos, M.P., Rihmer, Z., Mar 2010. Smoking, nicotine and neuropsychiatric disorders. Neurosci. Biobehav. Rev. 34 (3), 295–342.

Edwards, A.C., Maes, H.H., Pedersen, N.L., Kendler, K.S., Feb 2011. A population-based twin study of the genetic and environmental relationship of major depression, regular tobacco use and nicotine dependence. Psychol. Med. 41 (2), 395–405.

Egerton, A., Stone, J.M., Chaddock, C.A., et al., Nov 2014. Relationship between brain glutamate levels and clinical outcome in individuals at ultra high risk of psychosis. Neuropsychopharmacology 39 (12), 2891–2899.

Falkenberg, I., Valmaggia, L., Byrnes, M., et al., 2015. Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? Psychiatry Res. 228 (3), 808–815.

Fusar-Poli, P., Tantardini, M., De Simone, S., et al., Feb 2017. Deconstructing vulnerability for psychosis: meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. Eur. Psychiatry 40, 65–75.

Fusar-Poli, P., Salazar de Pablo, G., Correll, C.U., Jul 1 2020. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiat. 77 (7), 755–765.

Gage, S.H., Munafo, M.R., Feb 2015. Rethinking the association between smoking and schizophrenia. Lancet Psychiatry 2 (2), 118–119.

Gilbody, S., Peckham, E., Bailey, D., et al., May 2019. Smoking cessation for people with severe mental illness (SCIMITAR): a pragmatic randomised controlled trial. Lancet Psychiatry 6 (5), 379–390.

Gogos, A., Skokou, M., Ferentinou, E., Gourzis, P., 2019. Nicotine consumption during the prodromal phase of schizophrenia - a review of the literature. Neuropsychiatr. Dis. Treat. 15, 2943–2958.

Goldman, H.H., Skodol, A.E., Lave, T.R., Sep 1992. Revising axis V for DSM-IV: a review of measures of social functioning. Am. J. Psychiatry 149 (9), 1148–1156.

Gupta, T., Mittal, V.A., 2014. Nicotine usage is associated with elevated processing speed, spatial working memory, and visual learning performance in youth at ultrahigh-risk for psychosis. Psychiatry Res. 220 (1–2), 687–690.

Gurillo, P., Jauhar, S., Murray, R.M., MacCabe, J.H., 2015. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry 2 (8), 718–725, 2015/08/01/.

Harrison, X.A., Donaldson, L., Correa-Cano, M.E., et al., 2018. A brief introduction to mixed effects modelling and multi-model inference in ecology. PeerJ. 6, e4794.

Hu, Y., Fang, Z., Yang, Y., Rohlsen-Neal, D., Cheng, F., Wang, J., Feb 13 2018. Analyzing the genes related to nicotine addiction or schizophrenia via a pathway and network based approach. Sci. Rep. 8 (1), 2894.

Huang, H., Dong, M., Zhang, L., et al., 2019. Psychopathology and extrapyramidal side effects in smoking and non-smoking patients with schizophrenia: systematic review and meta-analysis of comparative studies. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 92, 476–482.

Kendler, K.S., Lonn, S.L., Sundquist, J., Sundquist, K., 2015. Smoking and schizophrenia in population cohorts of swedish women and men: a prospective co-relative control study. Am. J. Psychiatry 172 (11), 1092–1100.

Kotov, R., Guey, L.T., Bromet, E.J., Schwartz, J.E., Jan 2010. Smoking in schizophrenia: diagnostic specificity, symptom correlates, and illness severity. Schizophr. Bull. 36 (1), 173–181.

Kraan, T.C., Velthorst, E., Themmen, M., et al., 2018. Child maltreatment and clinical outcome in individuals at ultra-high risk for psychosis in the EU-GEI high risk study. Schizophr. Bull. 44 (3), 584–592.

Kumari, V., Postma, P., 2005. Nicotine use in schizophrenia: the self medication hypotheses. Neurosci. Biobehav. Rev. 29 (6), 1021–1034.

Lee, S.Y., Kim, K.R., Park, J.Y., et al., Feb 2011. Coping strategies and their relationship to psychopathologies in people at ultra high-risk for psychosis and with schizophrenia. J. Nerv. Ment. Dis. 199 (2), 106–110.

Liebschutz, J.M., Buchanan-Howland, K., Chen, C.A., et al., Jun 2018. Childhood trauma questionnaire (CTQ) correlations with prospective violence assessment in a longitudinal cohort. Psychol. Assess. 30 (6), 841–845.

Lim, J., Rekhi, G., Rapisarda, A., et al., May 2015. Impact of psychiatric comorbidity in individuals at ultra high risk of psychosis - findings from the longitudinal youth at risk study (LYRIKS). Schizophr. Res. 164 (1–3), 8–14.

Liu, M., Jiang, Y., Wedow, R., Feb 2019. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat. Genet. 51 (2), 237–244.

Luke, S.G., Aug 2017. Evaluating significance in linear mixed-effects models in R. Behav. Res. Methods 49 (4), 1494–1502.

Menghini-Muller, S., Studerus, E., Ittig, S., et al., Jun 2019. Gender differences of patients at-risk for psychosis regarding symptomatology, drug use, comorbidity and functioning - results from the EU-GEI study. Eur Psychiatry. 59, 52–59.

Mian, L., Lattanzi, G.M., Tognin, S., Aug 2018. Coping strategies in individuals at ultra-high risk of psychosis: a systematic review. Early Interv. Psychiatry. 12 (4), 525–534.

Moon, E., Chang, J.S., Choi, S., et al., 2014. Characteristics of stress-coping behaviors in patients with bipolar disorders. Psychiatry Res. 218 (1–2), 69–74.

Morrison, A.P., French, P., Stewart, S.L., Apr 5 2012. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 344, e2233.

Mustonen, A., Ahokas, T., Nordstrom, T., et al., Jul 2018. Smokin' hot: adolescent smoking and the risk of psychosis. Acta Psychiatr. Scand. 138 (1), 5–14.

Myles, N., Newall, H.D., Curtis, J., Nielssen, O., Shiers, D., Large, M., Apr 2012. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. J. Clin. Psychiatry 73 (4), 468–475.

Oluwoye, O., Monroe-DeVita, M., Burduli, E., et al., Feb 2019. Impact of tobacco, alcohol and cannabis use on treatment outcomes among patients experiencing first episode psychosis: data from the national RAISE-ETP study. Early Interv. Psychiatry 13 (1), 142–146.

Organization WH, 2017. WHO Report on the Global Tobacco Epidemic, 2017: Monitoring Tobacco Use and Prevention Policies. World Health Organization, Geneva (2017).

Parikh, V., Kutlu, M.G., Gould, T.J., Mar 2016. nAChR dysfunction as a common substrate for schizophrenia and comorbid nicotine addiction: current trends and perspectives. Schizophr. Res. 171 (1–3), 1–15.

Schizophrenia ENoNNsG-EIi, van Os, J., Rutten, B.P., Jul 2014. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr. Bull. 40 (4), 729–736.

Seltman, H.J., 2012. Online at:. In: Experimental Design and Analysis, 153, pp. 168–172 http://www.stat.cmu.edu/,hseltman/309/Book/Book.pdf.

Sterne, J.A., White, I.R., Carlin, J.B., Jun 29 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.

Taylor, G., Girling, A., Farley, A., Lindson-Hawley, N., Aveyard, P., McNeill, A., Feb 13 2014. Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ 348, g1151.

Turetsky, B.I., Dent, G., Jaeger, J., Zukin, S.R., 2012. P50 amplitude reduction: a nicotinic receptor-mediated deficit in first-degree relatives of schizophrenia patients. Psychopharmacology 221, 39–52, 2012/05/01.

Vermeulen, J., Schirmbeck, F., Blankers, M., 2019. Smoking, symptoms, and quality of life in patients with psychosis, siblings, and healthy controls: a prospective, longitudinal cohort study. Lancet Psychiatry 6 (1), 25–34, 2019/01/01/.

Volkow, N.D., May 2009. Substance use disorders in schizophrenia–clinical implications of comorbidity. Schizophr. Bull. 35 (3), 469–472.

Ward, H.B., Lawson, M.T., Addington, J., et al., Oct 2019. Tobacco use and psychosis risk in persons at clinical high risk. Early Interv. Psychiatry 13 (5), 1173–1181.

Wootton, R.E., Richmond, R.C., Stuijfzand, B.G., Nov 6 2019. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. Psychol. Med. 1–9.

Yung, A.R., Yuen, H.P., McGorry, P.D., Nov-Dec 2005. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust. N. Z. J. Psychiatry 39 (11–12), 964–971.

Zeng, L.N., Zong, Q.Q., Zhang, L., Jun 6 2020. Worldwide prevalence of smoking cessation in schizophrenia patients: a meta-analysis of comparative and observational studies. Asian J. Psychiatr. 54, 102190.