Smoking initiation and schizophrenia: a replication study in a Spanish sample

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Abstract

In a prior US study, schizophrenia vulnerability was associated with higher risk of initiating daily smoking after 20 years of age. A survival analysis of onset age of daily smoking compared 290 controls with 250 consecutive DSM-IV schizophrenia patients from outpatient facilities at an urban catchment area in Spain. After controlling for gender and education, the cumulative hazard curves for smoking initiation age of controls and schizophrenia patients were significantly different. After age 20, smoking initiation rates were higher in all schizophrenia patients (and in 107 schizophrenia patients who started daily smoking at least 5 years before illness onset).

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1. Introduction

A body of evidence suggests the hypothesis that schizophrenia may be associated with an increased vulnerability to start smoking (de Leon, 1996). For instance, schizophrenia is associated with relatively high ever smoking rates, and most patients with schizophrenia start smoking before illness onset. Six studies conducted in four different countries found that prevalences of ever smoking in schizophrenia patients were significantly higher than those in the general population (average odds ratio, OR=3.8, 95% confidence interval, CI=2.8–4.8) (Martínez-Ortega et al., 2004). Furthermore, when combining four studies from four different countries, ever smoking prevalence in schizophrenia patients was significantly higher than that in other severe mentally ill patients (OR=1.6, CI=1.2–2.1) (Martínez-Ortega et al., 2004).
A US study provided further evidence favoring the above hypothesis. It compared the age of onset of daily smoking (AODS) in schizophrenia patients versus people from the general population, and versus patients with other mental illnesses (de Leon et al., 2002), and suggested that people with schizophrenia or vulnerability to schizophrenia have higher risk of initiation of daily smoking after 20 years of age. The study used multivariate techniques that controlled for the potentially confounding effects of gender and education. The current study’s objective was to replicate the above analysis of daily smoking onset age with Spanish subject samples.

2. Subjects and method

2.1. Subjects

The study was located at two Community Mental Health Centers and a rehabilitation program covering the city of Granada (south of Spain). All patients received free psychiatric treatment from the national health system, which is divided in catchment areas including in- and out-patient facilities. This outpatient sample has been previously described (Gurpegui et al., in press), and included the first 250 consecutive patients who were diagnosed with DSM-IV schizophrenia (18 of 268 patients refused). The diagnosis was made by a research psychiatrist with the clinician version of a structured diagnostic interview (First et al., 1994). All patients were Caucasian. The mean age was 36.1 (S.D.=9.5) years, and age at diagnosis was 21.9 (S.D.=6.0). A patient’s age at diagnosis was defined as the age at which the patient was seen for the first time for psychiatric symptoms that led to a final diagnosis of schizophrenia.

There were 195 males (78%). Nine percent (23/250) of patients had college education. Most patients (94%, 236/250) were taking antipsychotics and many were on typical antipsychotics (71%, 171/250). The mean chlorpromazine equivalents dose (American Psychiatric Association, 1997) in those taking antipsychotics was 550 mg/day (S.D.=459).

A sample of controls without psychotic mental illnesses (N=290) included medical patients, relatives of other medical patients, and staff from a family medicine clinic who were studied with the 28-item General Health Questionnaire (GHQ-28) (Lobo et al., 1986). Psychotic mental illnesses were excluded after asking about prior or current psychiatric treatment. One person with a bipolar disorder and 3 with schizophrenia were excluded from the control group but persons with non-psychotic mental disorders were included. Controls’ mean age was 40.5 (S.D.=15.1) years and 113 controls were males (39%). Forty-nine percent (141/290) of controls had college education.

The prevalence of current smoking in controls (35%, Table 1) was the same as that found in a recent study of the Spanish general population (Pinilla and González, 2001). All patients and controls provided written informed consent after a complete study description.

2.2. Method

As in the prior study (de Leon et al., 2002), all subjects were asked to establish their tobacco smoking history. Subjects were asked about 1) ever daily smoking, defined as smoking on a daily basis during some period in life; 2) current daily smoking; 3) age of onset of daily smoking (AODS); and 4) high nicotine dependence, defined as a score ≥6 in the Fagerström Test for Nicotine Dependence (FTND) (Fagerstrom et al., 1996). The education level variable was split into high (having college) or low (Table 1). Unadjusted odds ratios (ORs) that compared schizophrenia patients with controls were calculated through cross-tabulations, and ORs adjusted for gender and education through logistic regressions (Table 1).

As in the US study (de Leon et al., 2002), initiation of daily smoking was explored through an AODS survival analysis. For a particular age, the smoking initiation rate is defined as the hazard rate and is measured by the slope of the cumulative hazard curve at that age (Fig. 1). The hazard rate for a particular age is the proportion per time unit of people who never smoked before that particular age, and who will start to smoke at that specific age (Klein and Moeschberger, 1997). Log-rank stratified tests for differences between cumulative hazard curves were conducted, controlling for gender and education level (Klein and Moeschberger, 1997; de Leon et al., 2002).
To rule out the possibility that these results may be explained by prodromal changes, initiation of psychiatric treatment, patient imitation or institutionalization, the controls’ cumulative hazard curve was

![Graph](image-url)
compared to that of those patients who started smoking before the prodromal period onset. The literature usually considers prodromal period to last up to one year (Elkhazen et al., 2003). McGlashan (2003) assumes that it may last 1 or 2 years. Following this assumption, the cumulative hazard curve for controls was initially compared with that of those patients who started smoking at least 2 years before illness onset. To take into account the possibility that some patients may have prodromal periods longer than 2 years, this comparison was repeated with only schizophrenia patients who started smoking at least 3, 4 and 5 years before illness onset.

3. Results

As expected, when compared with control subjects, schizophrenia patients had significantly higher prevalences of ever daily smoking (OR=2.1), current daily smoking (OR=4.3) as well as high nicotine dependence (OR=8.1) and heavy smoking (OR=3.9) among current daily smokers (Table 1). After adjusting for gender and education, the ORs for current daily smoking in all subjects, and for high nicotine dependence and heavy smoking in all current smokers were still significant (Table 1). Both adjusted and unadjusted ORs for current daily smoking and high nicotine dependence were significant within males, females and people with low or high educational level (Table 1).

The cumulative hazard curve for all schizophrenia patients was significantly different from controls, even after controlling for gender and educational level (Fig. 1). After 20 years of age, schizophrenia patients had significantly higher smoking initiation rates than controls (see Fig. 1 caption).

The cumulative hazard curve for patients who started daily smoking at least 5 years before illness onset (N=107) continued to be significantly different from controls, even after controlling for gender and education (Fig. 2). As before, after 20 years of age, initiation rates for schizophrenia patients were significantly higher (see Fig. 2 caption). Similar results were obtained for at least 4 years (N=118; stratified log-rank $\chi^2=88.9$, $df=1$, $p<0.001$), 3 years (N=129; stratified log-rank $\chi^2=84.9$, $df=1$, $p<0.001$) and 2

4. Discussion

The main conclusion of this Spanish study is that if a non-smoker with schizophrenia or vulnerable to schizophrenia is older than 20, the probability for him/her to become a daily smoker is higher than that for a comparably aged non-smoker from the general population. This conclusion suggests that some people vulnerable to schizophrenia are prone to become daily smokers later in their 20s, when other people rarely initiate daily smoking. The AODS comparison of controls and those schizophrenia patients who started smoking at least 5 years before their illness onset suggested that the observed differences in initiation rates between controls and patients were probably not due to prodromal changes or psychiatric treatment.
The above conclusions are consistent with those from the previous US study (de Leon et al., 2002) and supported our hypothesis that a vulnerability to schizophrenia may be associated with an increased vulnerability to start smoking (de Leon, 1996). As a matter of fact there is some information suggesting that this may be the case. Freedman et al. (1997) described a genetic neurophysiological abnormality in patients with schizophrenia (and their relatives), which is temporarily corrected by a high peak of nicotine. This abnormality is associated with a dysfunction of a specific hippocampal nicotine receptor (\(\alpha_7\)). More recently, Leonard et al. (1998) found that the presence of an \(\alpha_7\) promoter polymorphism was more frequent in schizophrenia patients than in controls and may be a marker of the neurophysiological abnormalities that increase the risk of schizophrenia.

Our results differ from those in a cohort study in Swedish male conscripts aged 18 to 20 years that suggested smoking may have a protective effect against the development of schizophrenia in patients with a illness onset between 20 and 25 years of age (Zammit et al., 2003). That study was limited by the exclusion of all females and of males who started schizophrenia before conscription; and by the lack of information on smoking initiation in males after 20 years old, which is crucial to establishing significant differences between male controls and male schizophrenia patients, according to our results.

Our analysis including patients with schizophrenia who started to smoke as early as 5 years before onset of schizophrenia suggests that the association between smoking and schizophrenia cannot be explained by the illness or prodromal period. The literature describes that some schizophrenia precursors such as minor neurological deficits may be present in early childhood and some speculate that neuropathological changes such as neuronal migration disturbances may occur before birth. However, neither the precursors nor the prenatal neuropathological disturbances are specific to schizophrenia, and probably many subjects who have them never develop schizophrenia. Thus, it appears to be better to consider precursors and prenatal neuropathological changes as risk factors for schizophrenia. Obviously, if one defends an extreme view (not shared by us) that schizophrenia illness includes the precursors and early neuropathological changes, both of these changes happen quite earlier than smoking initiation and one would have to consider the increased smoking initiation in patients with schizophrenia as another early sign of the illness.

5. Conclusion

This Spanish replication of US results suggests that vulnerability to schizophrenia may be associated with a higher risk of becoming a daily smoker. Prospective studies of patients with first psychotic episodes or subjects at risk of developing schizophrenia may be required to better establish the interaction between schizophrenia vulnerability, AODS and onset age of schizophrenia.

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