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Short communication

Snus use and risk of schizophrenia and non-affective psychosis

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ABSTRACT

Background: Recent studies suggest a possible causal role for smoking in schizophrenia and psychosis. Most studies have focused on cigarette smoking, the most common form of tobacco use, but other forms of tobacco exist, including smokeless products such as Swedish snuff (or "snus").
Methods: We explored whether snus use is associated with schizophrenia and non-affective psychotic illness in a large Swedish registry data set. The majority of participants were aged 18 or 19 at the time of assessment.
Results: We observed a positive association between snus use and odds of schizophrenia in all analyses, but the magnitude of the association was small and the confidence interval wide, consistent with no association (fully adjusted HR 1.03, 95% 0.70–1.54). A similar pattern was observed for non-affective psychosis, but the magnitude of the association was somewhat greater and the confidence intervals narrower, so that these analyses provided stronger statistical evidence for this association (fully adjusted HR 1.22, 95% CI, 1.00–1.48).
Conclusions: Our results therefore provide modest evidence for an association between snus use and risk for non-affective psychosis. This is consistent with emerging evidence from a range of studies and methodologies that tobacco use may be a risk factor for psychotic illness. However, our results provide some evidence against the hypothesis that it is the burnt products of cigarette smoke that are psychotogenic.

1. Introduction

Tobacco use prevalence is considerably higher among psychiatric patients, including people with schizophrenia, compared with the general population (de Leon and Diaz, 2005). For the most part, it has been assumed that this comorbidity reflects, at least in part, self-medication on the part of individuals with schizophrenia, to remediate either the symptoms of the disease, or the side-effects of antipsychotic medication. The possibility that the association may reflect a causal effect of tobacco use on schizophrenia risk has not received widespread consideration, despite the fact that tobacco use typically predates the onset of psychotic symptoms. If smoking is indeed a causal risk factor for schizophrenia, then this has important implications for public health, prevention and treatment.

A recent genome-wide association study of schizophrenia (Schizophrenia-Working-Group-of-the-Psychiatric-Genomics-Consortium, 2014) identified a locus in the *CHRNA5-A3-B4* gene cluster on chromosome 15, which has been consistently shown to be associated with heaviness of smoking (Tobacco-and-Genetics-Consortium, 2010). One possible explanation for this finding is that this signal captures a *causal* effect of cigarette smoking on schizophrenia (Gage and Munafo, 2015). There is a precedent for this pattern of results: the same region was shown to be associated with lung cancer risk (Thorgeirsson et al., 2008) but it is likely that this effect arises entirely via cigarette smoking (Munafo et al., 2012).

Intriguingly, several other recent studies have been published which also support a causal role for smoking in schizophrenia and psychosis (Gurillo et al., 2015; Kendler et al., 2015; McGrath et al.,

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2015; Wium-Andersen et al., 2015). One study reported a stratified analysis which suggests an association of *CHRNA5-A3-B4* genotype with antipsychotic medication prescription (as a proxy of psychotic illness) in ever smokers but not in never smokers (Wium-Andersen et al., 2015). Another used Swedish registry data to show that cigarette smoking predicted subsequent diagnosis of schizophrenia, and this association was not substantially altered either by potential confounders either using standard regression methods or co-relative analyses, or by the inclusion of a buffer period to account for the possibility that prodromal symptoms of schizophrenia prior to a diagnosis might lead to the uptake of smoking (Munafo et al., 2012).

Most studies to date have focused on cigarette smoking, largely because this is by far the most common form of tobacco use. However, other forms of tobacco use exist, such as smokeless forms including oral preparation such as Swedish snuff (or "snus"). Snus is a most powder tobacco product, typically sold in prepackaged pouches and usually placed under the upper lip. In general, snus use is associated with lower levels of harm than cigarette smoking (Le Houezec et al., 2011), although the evidence with respect to psychiatric outcomes is limited. We therefore explored whether a similar pattern of association is seen between snus use and schizophrenia and non-affective psychotic illness in a large Swedish registry data set. There is clear evidence that schizophrenia lies at the end of a continuum of vulnerability to psychotic-like symptoms and psychosis. Including non-affective psychosis therefore allowed us to increase statistical power while still addressing our underlying question.

2. Methods

2.1. Participants

We linked nationwide Swedish registers via the unique 10-digit identification number assigned at birth or immigration to all Swedish residents. The identification number was replaced by a serial number to ensure anonymity. Our database contained the following sources: the Multi-Generation Register, the Swedish Hospital Discharge Register, the Swedish Prescribed Drug Register, the Outpatient Care Register, the Primary Health Care Register, the Swedish Crime Register, the Swedish Suspicion Register, the Military Conscription Register, the Population and Housing Censuses, and the Total Population Register. More information on these data sources is provided as Supplementary material. Males with valid snus and smoking assessments, aged 18–25 at the time of conscription were eligible for inclusion. During the period sampled, all Swedish males were required by law to attend two days of evaluation for conscription. Only individuals with prior disabilities or serious criminal or behavioral disturbances were exempted. Around 97% of males are included in this sample. End of follow-up was the last year of information available, which for most registries was 2010.

2.2. Measures

We identified smoking and snus habits in young males from the Military Conscription Register. Snus use was assessed as "Yes" or "No", while smoking was assessed as follows: (1) "Not smoking", (2) Light smoking—(Winkleby et al., 2007) "1–10 cigarettes/day", or "1 packet of tobacco/week", (3) Average smoking—"11–20 cigarettes/day", or "1–2 packets/week", and (4) heavy smoking—">20 cigarettes/day", or ">2 packets/week." Schizophrenia (SZ) was defined in the Swedish Hospital Discharge Register by the following ICD 10 codes: F20.0, F20.1, F20.2, F20.3, F20.5, F20.8, and F20.9. Non-affective psychosis (NAP) was defined by the ICD 10 code: F2. More information on these codes is provided as Supplementary material.

Drug abuse (DA) was defined as follows: in the Swedish medical registries by ICD 10 codes: F10-F19, except (F10) or (F17); in the Suspicion Register by codes 3070, 5010, 5011, and 5012, that reflect crimes related to DA; and in the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DA was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A). These levels were set to be beyond what any responsible physician in Sweden would prescribe for anxiety or pain and would only arise from someone who is abusing the medications, often through getting multiple prescriptions from different physicians. This method of drug abuse assessment is validated by the strong correlation in probability of registration for drug abuse from medical and crime registries.

Family level socioeconomic status was assessed by low parental education, defined as elementary school only to index low educational attainment. Neighborhood level socioeconomic status was assessed by a composite measure of neighbourhood deprivation (Winkleby et al., 2007), which has been validated in prior studies (Chaikiat et al., 2012; Winkleby et al., 2007). In the year of conscription, this measure was classified into low, mid and high. This approach avoids problems associated with classifying socioeconomic status at the individual level, which may be impacted by current and recent behavior (e.g. drug use).

2.3. Statistical analysis

We investigated the association between snus and time to diagnosis in males not diagnosed with non-affective psychosis (including schizophrenia) before conscription with Cox proportional hazard methods, censoring at death or end of follow-up. The association between smoking and schizophrenia/non-affective psychosis is known and we therefore included the smoking × snus interaction in the model.

In addition to unadjusted analyses we adjusted for socioeconomic status, assessed as parental education at the individual level and neighbourhood deprivation, and DA before SZ/NAP onset. To facilitate interpretation, we present the snus associations separately by smoking category. Statistical analyses were performed using SAS 9.3 (18).

3. Results

3.1. Characteristics of participants

Of the 227,117 individuals fulfilling the inclusion criteria, 60,804 (26.8%) reported being snus users. The vast majority of participants (N = 223,412, 98.4%) were aged 18 or 19 at the time of assessment. A full description of the characteristics of participants, including snus users and non-users, is provided in Table 1.

3.2. Association of snus use with schizophrenia and non-affective psychosis

There was a positive association between snus use and odds of schizophrenia in all analyses, but the magnitude of the associations were small and the confidence intervals wide (unadjusted HR 1.13, 95% CI 0.77–1.67; partially adjusted HR 1.14, 955CI 0.77–1.68; fully adjusted HR 1.03, 95% 0.70–1.54) (Table 2). However, the small