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Smoking and Schizophrenia in Population Cohorts of Swedish Women and Men: A Prospective Co-Relative Control Study

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Abstract

Objective—The purpose of this study was to clarify the causes of the smoking-schizophrenia association.

Method—Using Cox proportional hazard and co-relative control models, the authors predicted future risk for a diagnosis of schizophrenia or nonaffective psychosis from the smoking status of 1,413,849 women and 233,879 men from, respectively, the Swedish birth and conscript registries.

Results—Smoking was assessed in women at a mean age of 27 and in men at a mean age of 18. The mean age at end of follow-up was 46 for women and 26 for men. Hazard ratios for first-onset schizophrenia were elevated both for light smoking (2.21 [95% CI=1.90–2.56] for women and 2.15 [95% CI=1.25–3.44] for men) and heavy smoking (3.45 [95% CI=2.95–4.03] for women and 3.80 [95% CI=1.19–6.60] for men). These associations did not decline when schizophrenia onsets 3–5 years after smoking assessment were censored. When age, socioeconomic status, and drug abuse were controlled for, hazard ratios declined only modestly in both samples. Women who smoked into late pregnancy had a much higher risk for schizophrenia than those who quit early. Hazard ratios predicting nonaffective psychosis in the general population, in cousins, in half siblings, and in full siblings discordant for heavy smoking were, respectively, 2.67, 2.71, 2.54, and 2.18. A model utilizing all relative pairs predicted a hazard ratio of 1.69 (95% CI=1.17–2.44) for nonaffective psychosis in the heavy-smoking member of discordant monozygotic twin pairs.

Conclusions—Smoking prospectively predicts risk for schizophrenia. This association does not arise from smoking onset during a schizophrenic prodrome and demonstrates a clear dose-response relationship. While little of this association is explained by epidemiological confounders, a portion arises from common familial/genetic risk factors. However, in full siblings and especially monozygotic twins discordant for smoking, risk for nonaffective psychosis is appreciably higher in the smoking member. These results can help in evaluating the plausibility of various etiological hypotheses for the smoking-schizophrenia association.

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The association between smoking and schizophrenia is strong and widely replicated. A meta-analysis of 42 cross-sectional studies examining current smoking in patients with schizophrenia and population controls estimated an odds ratio of 5.3 (1). Despite the strength of this association, its etiology remains unclear.

In this study, we attempted to address four questions about the smoking-schizophrenia association:

1. Does smoking predict the subsequent risk for schizophrenia? If so, could these results arise from smoking onset during prodromal phases of illness?
2. Is there a prospective dose-response relationship between smoking and risk for schizophrenia?
3. What proportion of the smoking-schizophrenia association arises from key potential confounders, particularly low socioeconomic status and drug abuse?
4. To what extent is the smoking-schizophrenia association due to shared familial/ genetic risk factors?

The prospective relationship between smoking and risk for schizophrenia has been studied twice, to our knowledge, with contradictory results. In a sample of 50,000 Swedish male conscripts with self-reported smoking assessed at ages 18–20 and followed up over 26 years, smoking was associated with a reduced risk for schizophrenia (2). By contrast, an Israeli study of 14,000 conscripts at ages 16–17 with follow-up over 4–16 years found that smoking was associated with a substantially increased risk for schizophrenia (3).

A dose-response relationship is one important criterion for a potentially causal relationship (4), and one was found for smoking and schizophrenia in the prospective Israeli study, using self-reported level of consumption (3). Could this be replicated and expanded to measures reflecting nicotine dependence?

Of the confounders that could explain the smoking-schizophrenia association, three are noteworthy: low socioeconomic status (5–7), drug abuse (8–11), and familial/ genetic factors (12, 13). Nicotinic receptor variants that predispose to smoking (14) increase risk for schizophrenia (15).

Here we report two prospective cohort studies of the smoking-schizophrenia association in 1.4 million Swedish women whose smoking status was evaluated during prenatal care, with a mean follow-up of more than 18 years, and 230,000 Swedish men whose smoking status was recorded in the conscript registry, with a mean follow-up of nearly 8 years. To address the four questions outlined above, we matched data from members of these cohorts to complete national health care data for subsequent diagnoses of schizophrenia and nonaffective psychosis.

METHOD

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. For details on the databases used, see the data supplement that accompanies the online edition of this article. We obtained ethical approval for the study from the Regional Ethical Review Board of Lund University. The date of onset of illness was defined as the first hospital discharge diagnosis for schizophrenia or nonaffective psychosis.

Measures

We identified smoking habits in women from the Swedish Birth Register, in which smoking was categorized as follows: not smoking, light smoking (1–9 cigarettes/day), or heavy smoking (≥10 cigarettes/day). Information on smoking status was recorded at the time of registration by the midwife (typically week 12 of pregnancy) from 1981, at week 30–32 from 1990, and before pregnancy from 1998. When multiple pregnancies were recorded, we used data from the first pregnancy for which adequate information was available. Smoking status in men was identified from the Military Conscription Register, in which smoking was categorized as follows: not smoking, light smoking (1–10 cigarettes/day, 1 packet of tobacco/week, or 1–2 packets/week), or heavy smoking (11–20 cigarettes/day, >20 cigarettes/day, or >2 packets/week). For the definitions used for schizophrenia, nonaffective psychosis, chronic obstructive pulmonary disease (COPD), lung cancer, and drug abuse, see the online data supplement.

Family-level socioeconomic status was assessed using low parental education as a marker, defined as having completed elementary school only. Community-level socioeconomic status was defined by a composite measure of neighborhood deprivation (16) that has been validated in studies predicting coronary heart disease (16, 17). In the year of smoking assessment, this measure was trichotomized into low, middle, and high values. Female-female relative pairs were identified from the Multi-Generation Register.

Statistical Analysis

We used Cox proportional hazard regressions to investigate the association between smoking and time to schizophrenia diagnosis in both the female and male samples, among those not diagnosed with non affective psychosis before first smoking assessment, censoring for death and end of follow-up. To evaluate the possibility that smoking began during a symptomatic prodromal period, we censored from our hazard models buffer periods (from smoking assessment to first counted onset) of 1, 3, and 5 years.

Next, in the female sample only, using smoking data from the birth registry, we used pairs of monozygotic twins, full siblings, half siblings, and cousins to perform a co-relative analysis. Schizophrenia was too rare in our sample to obtain stable estimates from these analyses, so we conducted them for nonaffective psychosis and, as a comparison, COPD. The association between smoking and outcome was modeled utilizing a stratified Cox regression in which each pair is treated as a stratum. We thereby estimated the association within pairs and controlled for shared genetic and environmental factors. Monozygotic twins share 100% of their genes, while full sisters, half sisters, and cousins share, respectively, on average 50%, 25%, and 12.5% of their genes by descent. We constructed a model including all four types of relative relationships, in which the hazard ratio for each relative type is dependent on the

degree of genetic resemblance. The logarithm of the hazard ratios is assumed to be a linear function of the proportion of genes shared and of smoking severity. The linearity assumption is evaluated by comparing the model's fit with a model in which the hazard ratios for the different relative types are independent, corresponding to separate analyses for the four co-relative relationships. If the linear model is appropriate, we would obtain an improved estimate of the association among monozygotic twins, a subsample in which the data are sparse (only six monozygotic pairs were discordant on smoking and nonaffective psychosis). Statistical analyses were performed in SAS, version 9.3 (SAS Institute, Cary, N.C.).

RESULTS

Does Smoking Predict Subsequent Risk for Schizophrenia?

Smoking status at first midwife assessment from the birth registry was available for 1,413,849 women with no prior history of nonaffective psychosis. (For all other relevant sample sizes, see online data supplement.) Their mean age at first assessment was 27.3 years (SD=5.2), and their mean followup period was 18.5 years (SD=8.4). InTable 1 and Figure 1, we first present raw hazard ratios for future episodes of schizophrenia associated with light smoking (hazard ratio=2.21, 95% CI=1.90–2.56) and heavy smoking (hazard ratio=3.45, 95% CI=2.95–4.03).

Smoking data were available for 233,879 men with no prior diagnosis of nonaffective psychosis, as part of their evaluation for army conscription between 2002 and 2008. Their mean age at evaluation was 18.3 years (SD=0.6), and their mean follow-up period was 7.9 years (SD=1.9). We analyzed the observed association between light and heavy smoking and subsequent risk for schizophrenia in the same manner as with the female sample (Table 2 and Figure 1). The raw hazard ratios for future episodes of schizophrenia in this sample were 2.15 (95% CI=1.25–3.44) for light smoking and 3.80 (95% CI=1.19–6.60) for heavy smoking.

Could This Association Arise From Smoking Onset During Illness Prodrome?

Smoking could have occurred as part of a prodromal schizophrenic syndrome. Therefore, we assessed the predictive effect of smoking after building in a buffer period from smoking assessment to the date at which a first schizophrenia diagnosis would be counted. If the smoking-schizophrenia association arose largely from smoking onset during the prodrome, this association should attenuate substantially with progressively longer buffer periods. Table 1 shows results for 1-, 3-, and 5-year buffer periods for the female sample. The smoking-schizophrenia association did not decline with longer buffer periods. Because of the shorter follow-up time, we examined buffer periods of only 1 and 3 years in the male sample (Table 2). Again, no consistent trend was seen.

Is There a Dose-Response Relationship Between Smoking and Risk for Schizophrenia?

In both our female and male samples, risk for schizophrenia was more strongly associated with heavy than with light smoking. We sought to validate our smoking exposure in the female sample, which both was larger and had a much longer follow-up period. Could we show that the heavy-smoking group indeed had greater smoke exposure than our light

smoking group? Odds ratios for subsequent onset of lung cancer in this sample were 4.31 (95% CI=3.75–4.96) for light smoking and 8.18 (95% CI=7.17–9.34) for heavy smoking. For the more commonly occurring COPD, the odds ratios were 4.63 (95% CI=4.38–4.90) and 9.39 (95% CI=8.89–9.91), respectively.

We explored another measure of smoking severity as a proxy for nicotine dependence, namely, smoking behavior just before and in early and late pregnancy. A total of 643,968 women reported their smoking status prior to the start of their pregnancy, and 763,899 women reported their smoking status at week 30–32. Compared with the smoking rate at their first prenatal visit, typically at week 1 or 2 (19.4%), smoking was slightly more common prior to pregnancy (21.9%) and much lower at week 30–32 (10.1%). In the subset of our sample seen in 1999 and later, when smoking was assessed at all three time points, we constructed five categories that likely reflect increasing levels of nicotine dependence (Table 3). For example, women in category 1 only smoked lightly before becoming pregnant and quit before their first midwife visit. Those in category 5, by contrast, were smoking heavily at week 30–32. For COPD, substantially increased risks were seen for women in categories 3 to 5, so we can infer that it was these groups that had the highest lifetime smoke exposure. For schizophrenia, a significantly increased risk was restricted to women in categories 4 and 5, and for nonaffective psychosis, increased risk was seen for women in categories 2 to 5.

Does the Smoking-Schizophrenia Association Arise From Key Potential Confounders?

As seen in Table 1 and Figure 1, when we added covariates that reflected neighborhood and parental socioeconomic status to the regression model in our female sample, the hazard ratios between smoking and schizophrenia were slightly lower (2.16 and 3.35, respectively). Drug abuse, another potential confounder, was present in 4.8% (95% CI=4.7–4.9) of the smoking women and 0.8% (95% CI=0.8–0.9) of the nonsmoking women in our sample. Adding registration for prior drug abuse to the model further reduced the hazard ratios, although modestly (to 1.92 and 2.77, respectfully). As seen in Table 2 and Figure 1, adding controls for family-level and community-level socioeconomic status results in our male sample also resulted in a modest diminution of the smoking schizophrenia association (to hazard ratios of 2.05 and 3.45, respectively). A somewhat greater reduction in hazard ratios was seen in the male sample when we added prior registration for drug abuse to the model (to 1.62 and 2.21, respectively), perhaps because of the higher prevalence in this sample (22.4% [95% CI=21.9–22.8] for the smokers and 4.0% [95% CI=3.9–4.1] for the nonsmokers).

Does the Smoking-Schizophrenia Association Arise From Shared Familial/Genetic Risk Factors?

We next conducted co-relative analyses to examine the degree to which the smoking-schizophrenia association could be explained by shared familial/genetic risk factors. We compared the association between smoking and schizophrenia in our female cohort to the associations observed within pairs of relatives of increasing genetic relatedness who had been selected on the basis of discordance for smoking. If the smoking-schizophrenia association arises largely from shared familial/genetic risk factors, the magnitude of that association should decline within pairs of increasing familial/genetic relationship. As most

easily seen inmonozygotic twins discordant for smoking, if smoking and schizophrenia co-occur because of the effect of a common set of risk genes, the risk for schizophrenia should be the same in the smoking and the nonsmoking member of such a pair, as they share all of their genes.

Because the rarity of schizophrenia in this sample resulted in unstable statistical estimates, we emphasize our analyses of nonaffective psychosis and, for comparison, COPD. To simplify the interpretation of these findings, we estimated the hazard ratio per one-unit increase in the three-level risk factor of nonsmoking, light smoking, and heavy smoking.

In Table 4, we present the descriptive hazard ratios estimated from the entire population and from full sisters, half sisters, and female cousins discordant for smoking. No appreciable difference is seen in the magnitude of the smoking nonaffective psychosis association in the general population and in cousins. Modest decreases are seen in half and full siblings.

To estimate the critical results in monozygotic pairs, we fitted a model based on four sets of relative pairs: first cousins, half siblings, full siblings, and monozygotic twin pairs (Table 5). For both nonaffective psychosis and COPD, a model that constrained these hazard ratios to be dependent on genetic resemblance only slightly changed the within-pair estimates and, as detailed in the footnotes to Table 5, fit the data well. For nonaffective psychosis, this model predicted a significant association within discordant monozygotic twins between smoking and nonaffective psychosis. Where one member of a monozygotic twin pair is a non smoker and the other a smoker, the model predicts a relative risk for nonaffective psychosis, respectively, 30% higher for the light-smoking co-twin and 69% higher for the heavy-smoking co-twin (the confidence intervals do not include unity for either of these estimates).

For interest, we also present results for COPD, which has a well-established causal association with smoking. The pattern is similar, although the association is stronger overall.

Analogous to results presented for nonaffective psychosis in Table 4, we calculated the hazard ratio for schizophrenia in the entire sample (3.58, 95%CI=3.10–4.15) and in cousins (3.87, 95% CI=2.86–5.25), half sisters (4.75, 95% CI=2.27–9.91), and full sisters (2.27, 95% CI=1.59–3.23) discordant for heavy smoking. While known less precisely, the trend—showing moderate familial confounding insisters but none in cousins or half sisters—is similar to that seen for nonaffective psychosis.

DISCUSSION

We sought in this study to address four important questions about the smoking-schizophrenia association. We review our findings on each in turn.

Prospective Prediction of Risk

We first sought to examine whether smoking predicted subsequent risk for schizophrenia. We found clear evidence for such an effect in both our male and female samples. Despite differences in sex and age, the magnitudes of the associations were similar in both cohorts. Our findings are congruent with those reported by Weiser et al. (3) in Israeli army recruits. Our results are also consistent with a longitudinal study of the British National Psychiatric

Morbidity Survey (18) that found, in a multivariate analysis of multiple risk factors, smokers to be at nearly twice the risk for incident psychotic symptoms. By contrast, our results are discordant with those reported by Zammit et al. (2) in a smaller sample of Swedish army recruits in 1969 and 1970, which was not part of the cohort studied here.

A plausible explanation for the prospective association of smoking and schizophrenia is that smoking initiation is part of the schizophrenia prodrome. To evaluate this hypothesis, we examined whether the association declined when a buffer period was built into the analysis between smoking assessment and schizophrenia onset. Consistent with previous work (19), we found no appreciable decline in either the female or the male cohort.

Taken together, these results strongly suggest that smoking prospectively increases the risk for schizophrenia onset. This is an important result because it provides critical information about the potential causes of the smoking-schizophrenia association.

Dose-Response Relationship

Our second question was whether we could demonstrate a dose-response relationship between smoking and risk for schizophrenia. Consistent with such an effect, in both our samples, the risk for schizophrenia was substantially higher in heavy smokers than in light smokers as defined using the standard measure of average consumption of cigarettes per day. These findings are also congruent with those reported by Weiser et al. (3) in the Israeli army recruits. We were also able to validate our smoking measures (including a greater exposure in the heavy compared with the light smokers) by showing robust dose-response associations with future risk for lung cancer and COPD, of magnitudes consistent with findings from previous epidemiological studies (20, 21).

We were furthermore able to take advantage of a natural experiment to evaluate a different kind of dose-response relationship. We had smoking measures at three time points in our sample of fertile women: before pregnancy, at first visit to the nurse midwife during the first trimester, and at week 30–32. In addition to the social pressure on pregnant women to quit smoking, the nurse midwives also typically counsel Swedish women on the adverse fetal effects of smoking. In epidemiological samples, declining rates of smoking are associated with increasing rates of nicotine dependence in those still smoking (22). We suspect that a similar effect occurred in our pregnant women, such that those who were still smoking in their third trimester were more nicotine dependent than those who quit earlier. As predicted by this hypothesis, we found much higher rates of future COPD in women who were still smoking in their third trimester, indicating high levels of smoke exposure. It was also in those women that we found the highest rate of schizophrenia.

These results, demonstrated using two distinct methods, are important because a dose-response relationship between a risk factor and an outcome has long been considered supportive of (but far from proof of) a causal relationship (4).

The Role of Confounders

Both socioeconomic status and drug abuse are plausible confounders that might be responsible for large proportions of the smoking-schizophrenia association. This is because

low socioeconomic status predicts risk for smoking (both in Swedish and U. S. women [5, 6]) and risk for schizophrenia (7). Drug abuse is also associated with high smoking rates and with risk for schizophrenia (10, 11). Using standard regression methods, when we controlled for both community-level and family-level socioeconomic status and registration for drug abuse, we found relatively modest declines in the smoking schizophrenia association in both our female and male cohorts.

The Role of Common Familial/Genetic Risk Factors

To assess whether common familial/genetic risk factors could account for the observed smoking-schizophrenia association, we utilized co-relative analyses. We focused our analyses on results for nonaffective psychosis, as the results were more stable than those obtained for the rarer schizophrenia outcome. However, Swedish psychiatry has a long tradition of a narrow diagnostic approach to schizophrenia. Consistent with this, Ekholm et al. (23) found that 41% of hospitalized Swedish patients diagnosed with other psychoses (most commonly schizoaffective disorder and psychosis not otherwise specified, both of which were in our category of nonaffective psychosis) met DSM-IV criteria for schizophrenia at diagnostic interview. Furthermore, previous studies have shown a strong familial/genetic relationship between narrow schizophrenia and nonaffective psychosis (24, 25).

The raw Cox results (Table 4) showed a decline in the smoking-nonaffective psychosis relationship in full siblings compared with more distant relatives or the general population. This is the pattern that would be expected if the association between smoking and nonaffective psychosis were partly a result of familial/genetic risk factors that predisposed to both smoking and nonaffective psychosis. However, the decline in hazard ratios across relatives of increasing affinity was modest. The smoking-nonaffective psychosis association remained robust even in smoking discordant full siblings. A steeper decline across classes of relatives would be expected if the association resulted entirely from familial confounding.

We formally tested this in a model that incorporated all available information on risk for schizophrenia across four groups of relatives: cousins, half siblings, full siblings, and monozygotic twins. Fitting the observed smoking-schizophrenia associations across types of relatives to those expected given their genetic relatedness, the model provided a good fit to the data. It predicted that the risk for nonaffective psychosis is substantially increased in the light-smoking and especially the heavy-smoking member of a monozygotic pair compared with their nonsmoking co-twin.

These results are important because they expand considerably the possible confounders that we evaluated for their impact on the smoking-schizophrenia association. Unlike regression methods, which must specify individual measured confounders, the co-relative design controls for *all* potential confounding variables that are familial, which includes a large proportion of all human traits and exposures. For example, given previous evidence for the high heritability of drug abuse (26–28), the co-relative design complements our more standard regression analysis in controlling for this confounding influence.

Limitations

These results should be interpreted in the context of three potentially important limitations. First, we do not have data on lifetime smoking status and therefore had to rely on evidence for increased risk for lung cancer and COPD as validating measures. Second, we used only clinical diagnoses. However, two previous studies found, using record reviews (29) and diagnostic interviews (23), that about 95%of Swedish cases with hospital diagnoses of schizophrenia met DSM-IV criteria. Third, we initially focused our analyses solely on schizophrenia and nonaffective psychosis and thus could not address the specificity of our findings. Therefore, we examined, using the same models, the prediction of first hospitalizations for bipolar illness by level of smoking in our female sample. The raw hazard ratios for light and heavy smoking were significant but substantially lower than those seen with schizophrenia—1.62 (95% CI=1.48–1.77) and 1.90 (95% CI=1.71–2.11), respectively—and they changed little when we controlled for family and community socioeconomic status. However, adding prior drug abuse reduced the observed association to modest levels: 1.16 (95% CI=1.03–1.30) and 1.25 (95% CI=1.09–1.44), respectively. Consistent with previous studies (1), the association of smoking with first diagnosis of bipolar illness was considerably weaker than that seen with schizophrenia, especially after the addition of critical covariates. These results suggest at least some specificity in the smoking-schizophrenia association.

CONCLUSIONS

The findings reported here are of particular value because they provide insights into the possible causal mechanisms underlying the smoking-schizophrenia association. There are three such mechanisms particularly worthy of attention: 1) schizophrenia causes smoking, 2) smoking causes schizophrenia, and 3) the association arises from risk factors common to both conditions (that is, confounders). We suggest three major conclusions. First, our results strongly suggest thatmechanism1 cannot explain the whole story, as in two large and diverse population samples we showed that smoking robustly predicted future risk for schizophrenia. The smoking-schizophrenia association cannot be explained solely as a result of some aspect of schizophrenia, including its symptoms or its treatment, increasing the risk of smoking onset. However, our prospective smoking-schizophrenia association was weaker than the best estimate of their association when assessed cross-sectionally (meta-analytic odds ratio=5.3 [1]). These findings might suggest that part of the smoking-schizophrenia association arises from increased initiation or decreased cessation of smoking after schizophrenia onset. Second, we found support for mechanism 3 with somewhat stronger evidence for familial/genetic factors than for the “leading suspect” epidemiological confounders of socioeconomic status and drug abuse. The declining association between smoking and schizophrenia in discordant relative pairs of increasing relatedness strongly suggests that shared familial/genetic factors account for part of the comorbidity between smoking and schizophrenia. Third, however, two of our findings provide support for mechanism 2 (30, 31). Examining both cigarettes smoked per day and an indirect but ecologically valid measure of nicotine dependence, we found a dose-response relationship between smoking and risk for schizophrenia. More importantly, in close relatives discordant for smoking, the smoking member was at an appreciably elevated risk for future

nonaffective psychosis. However, even our monozygotic twin results are not definitive, as they could arise from some environmental exposure that increases risk for both smoking and nonaffective psychosis but is not substantially correlated in pairs of close relatives like siblings or twins. But the plausibility of such exposures is uncertain, since most documented risk factors for schizophrenia, such as paternal age and cannabis exposure, are themselves highly familial (7, 32). Furthermore, we ourselves have shown that drug abuse is highly heritable in females in Sweden (73%) (28).

In summary, our findings suggest that the causes of the smoking-schizophrenia association are complex. Shared familial/genetic risk factors and, to a lesser extent, other epidemiological confounders contribute to the association. While a schizophrenia → smoking causal pathway cannot explain the entire association, we found indirect evidence for its importance. Most challenging and hopefully stimulating to further research is our evidence for the potential importance of a causal relationship between smoking and risk for schizophrenia (31).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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; 76:135–157. [PubMed: 15949648]
2. Zammit S, Allebeck P, Dalman C, et al. Investigating the association between cigarette smoking and schizophrenia in a cohort study. Am J Psychiatry. 2003; 160:2216–2221. [PubMed: 14638593]
3. Weiser M, Reichenberg A, Grotto I, et al. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. Am J Psychiatry. 2004; 161:1219–1223. [PubMed: 15229054]
4. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965; 58:295–300. [PubMed: 14283879]
5. Cavelaars AE, Kunst AE, Geurts JJ, et al. Educational differences in smoking: international comparison. BMJ. 2000; 320:1102–1107. [PubMed: 10775217]
6. Department of Health and Human Services. Rockville, Md: US Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001. Women and Smoking: A Report of the Surgeon General.
7. Matheson SL, Shepherd AM, Laurens KR, et al. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. Schizophr Res. 2011; 133:133–142. [PubMed: 21999904]
8. Lai S, Lai H, Page JB, et al. The association between cigarette smoking and drug abuse in the United States. J Addict Dis. 2000; 19:11–24. [PubMed: 11110061]
9. Torabi MR, Bailey WJ, Majd-Jabbari M. Cigarette smoking as a predictor of alcohol and other drug use by children and adolescents: evidence of the “gateway drug effect”. J Sch Health. 1993; 63:302–306. [PubMed: 8246462]

10. Arseneault L, Cannon M, Witton J, et al. Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry. 2004; 184:110–117. [PubMed: 14754822]
11. Giordano GN, Ohlsson H, Sundquist K, et al. The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. Psychol Med. (Epub ahead of print, July 3, 2014).
12. Lyons MJ, Bar JL, Kremen WS, et al. Nicotine and familial vulnerability to schizophrenia: a discordant twin study. J Abnorm Psychol. 2002; 111:687–693. [PubMed: 12428784]
13. Smith MJ, Barch DM, Wolf TJ, et al. Elevated rates of substance use disorders in non-psychotic siblings of individuals with schizophrenia. Schizophr Res. 2008; 106:294–299. [PubMed: 18774264]
14. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet. 2010; 42:441–447. [PubMed: 20418890]
15. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–427. [PubMed: 25056061]
16. Winkleby M, Sundquist K, Cubbin C. Inequities in CHD incidence and case fatality by neighborhood deprivation. Am J Prev Med. 2007; 32:97–106. [PubMed: 17234484]
17. Chaikiat Å, Li X, Bennet L, et al. Neighborhood deprivation and inequities in coronary heart disease among patients with diabetes mellitus: a multilevel study of 334,000 patients. Health Place. 2012; 18:877–882. [PubMed: 22498356]
18. Wiles NJ, Zammit S, Bebbington P, et al. Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey. Br J Psychiatry. 2006; 188:519–526. [PubMed: 16738341]
19. Diaz FJ, Velásquez DM, Susce MT, et al. The association between schizophrenia and smoking: unexplained by either the illness or the prodromal period. Schizophr Res. 2008; 104:214–219. [PubMed: 18650069]
20. Nordlund LA, Carstensen JM, Pershagen G. Cancer incidence in female smokers: a 26-year follow-up. Int J Cancer. 1997; 73:625–628. [PubMed: 9398036]
21. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis, and emphysema. BMC Pulm Med. 2011; 11:36. [PubMed: 21672193]
22. Irvin JE, Brandon TH. The increasing recalcitrance of smokers in clinical trials. Nicotine Tob Res. 2000; 2:79–84. [PubMed: 11072444]
23. Ekholm B, Ekholm A, Adolfsson R, et al. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. Nord J Psychiatry. 2005; 59:457–464. [PubMed: 16316898]
24. Kendler KS, Gruenberg AM, Tsuang MT. Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: a family study using DSM-III criteria. Arch Gen Psychiatry. 1985; 42:770–779. [PubMed: 4015321]
25. Kendler KS, McGuire M, Gruenberg AM, et al. The Roscommon Family Study, II: the risk of nonschizophrenic nonaffective psychoses in relatives. Arch Gen Psychiatry. 1993; 50:645–652. [PubMed: 8343035]
26. Tsuang MT, Lyons MJ, Eisen SA, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. Am J Med Genet. 1996; 67:473–477. [PubMed: 8886164]
27. Kendler KS, Jacobson KC, Prescott CA, et al. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am J Psychiatry. 2003; 160:687–695. [PubMed: 12668357]
28. Kendler KS, Maes HH, Sundquist K, et al. Genetic and family and community environmental effects on drug abuse in adolescence: a Swedish national twin and sibling study. Am J Psychiatry. 2014; 171:209–217. [PubMed: 24077613]
29. Lichtenstein P, Björk C, Hultman CM, et al. Recurrence risks for schizophrenia in a Swedish national cohort. Psychol Med. 2006; 36:1417–1425. [PubMed: 16863597]
30. Zullino DF, Manghi R, Rathelot T, et al. Cannabis causes schizophrenia? So does nicotine. Addict Res Theory. 2010; 18:601–605.

31. Gage SH, Munafo MR. Rethinking the association between smoking and schizophrenia. Lancet Psychiatry. 2015; 2:118–119. [PubMed: 26359739]

32. Kendler KS, Prescott CA. Cannabis use, abuse, and dependence in a population-based sample of female twins. Am J Psychiatry. 1998; 155:1016–1022. [PubMed: 9699687]

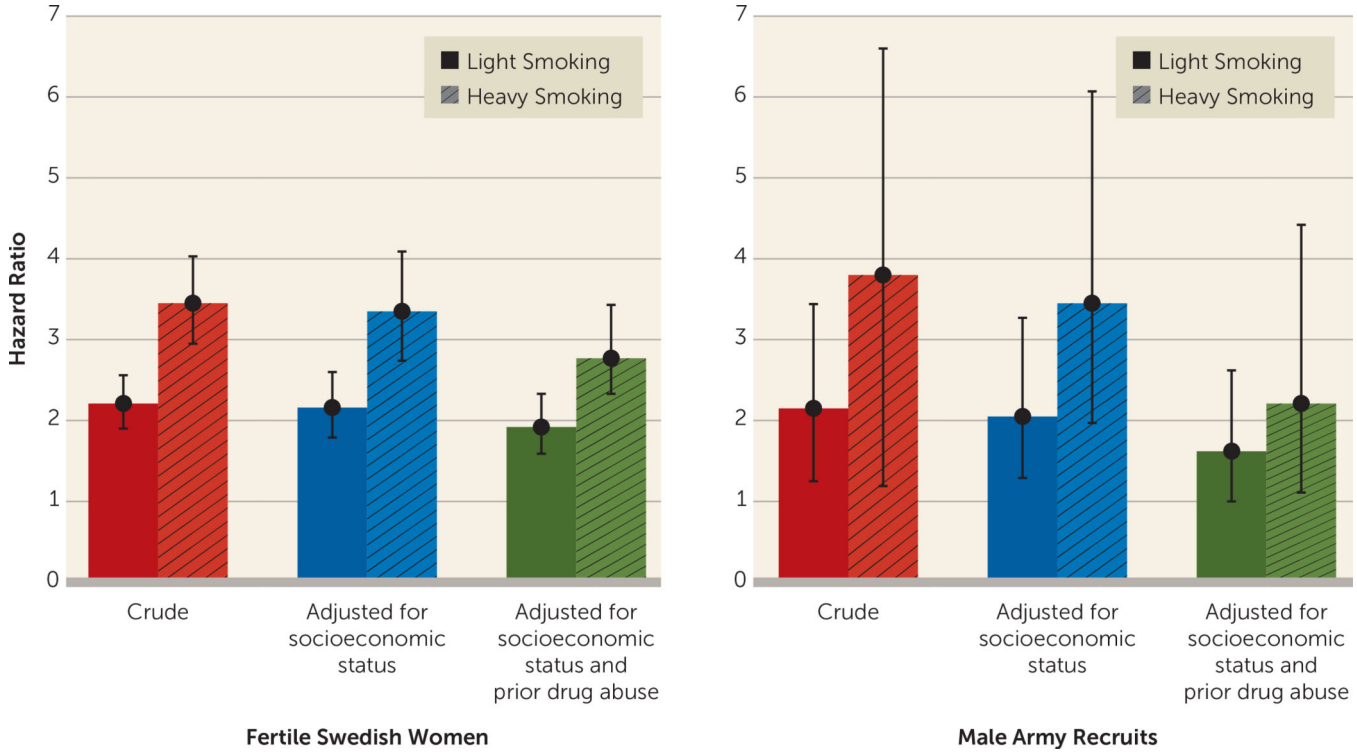

FIGURE 1.

Hazard Ratios for the Risk of Future Onset of Schizophrenia in Fertile Swedish Women and Male Army recruits, as Predicted by Light and Heavy Smoking Status[a]

[a] Adjustment for socioeconomic status is based on measures of both family socioeconomic status (as assessed by low parental education) and community socioeconomic status (as assessed by neighborhood deprivation). Adjustment for drug abuse is based on registration for drug abuse in any of several registries (see the online data supplement). Error bars indicate 95% confidence intervals.

TABLE 1

Hazard Ratio for First Diagnosis of Schizophrenia in Fertile Swedish Women as a Function of Level of Smoking and Buffer Period From Smoking Assessment to First Possible Diagnosis

		Hazard Ratio					
		Crude		Adjusted for Socioeconomic Status[a]		Adjusted for Socioeconomic Status and Prior Drug Abuse[a]	
Buffer Period	**Predictor Variable**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
0 years	1–9 cigarettes/day versus none	2.21	1.90, 2.56	2.16	1.79, 2.60	1.92	1.59, 2.33
	10 cigarettes/day versus none	3.45	2.95, 4.03	3.35	2.74, 4.09	2.77	2.34, 3.43
	Neighborhood deprivation (mid versus low)			1.87	1.43, 2.43	1.84	1.41, 2.39
	Neighborhood deprivation (high versus low)			2.00	2.56, 3.96	2.81	2.12, 3.73
	Low parental education			1.53	1.31, 1.79	1.56	1.34, 1.83
	Drug abuse					5.14	3.97, 6.65
1 year	1–9 cigarettes/day versus none	1.89	1.76, 2.04	2.19	1.81, 2.65	1.95	1.61, 2.37
	10 cigarettes/day versus none	3.58	3.09, 4.15	3.27	2.75, 4.12	2.78	2.24, 3.46
	Neighborhood deprivation (mid versus low)			1.82	1.40, 2.37	1.80	1.38, 1.34
	Neighborhood deprivation (high versus low)			2.90	2.19, 3.84	2.72	2.05, 3.61
	Low parental education			1.49	1.27, 1.74	1.52	1.30, 1.78
	Drug abuse					5.20	4.01, 6.75
3 years	1–9 cigarettes/day versus none	2.26	1.93, 2.63	2.22	1.82, 2.70	1.95	1.60, 2.39
	10 cigarettes/day versus none	3.43	2.91, 4.04	3.39	2.75, 4.19	2.77	2.21, 3.47
	Neighborhood deprivation (mid versus low)			1.78	1.35, 2.34	1.75	1.33, 2.30
	Neighborhood deprivation (high versus low)			2.83	2.11, 3.78	2.64	1.97, 3.55
	Low parental education			1.44	1.22, 1.79	1.47	1.25, 1.74
	Drug abuse					5.57	4.28, 7.28
5 years	1–9 cigarettes/day versus none	2.14	1.82, 2.53	2.13	1.72, 2.64	1.86	1.50, 2.31
	10 cigarettes/day versus none	3.38	2.85, 4.01	3.38	2.70, 4.22	2.71	2.13, 3.45
	Neighborhood deprivation (mid versus low)			1.88	1.40, 2.54	1.85	1.37, 2.49
	Neighborhood deprivation (high versus low)			2.92	2.13, 4.02	2.72	1.97, 3.75
	Low parental education			1.45	1.22, 1.73	1.49	1.25, 1.77
	Drug abuse					6.09	4.62, 8.05

[a] Adjustment included both family socioeconomic status (as assessed by low parental education) and community socioeconomic status (as assessed by neighborhood deprivation). Adjustment for drug abuse is based on registration for drug abuse in any of several registries (see the online data supplement).

TABLE 2

Hazard Ratio for First Hospitalization for Schizophrenia in Swedish Males As a Function of Level of Smoking and Time Lag From Smoking Assessment to First Possible Hospitalization

		Hazard Ratio					
		Crude		Adjusted for Socioeconomic Status[a]		Adjusted for Socioeconomic Status and Prior Drug Abuse[a]	
Time Lag	Predictor Variable	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
0 years	Light smoking versus none	2.15	1.25, 3.44	2.05	1.29, 3.27	1.62	1.00, 2.62
	Heavy smoking versus none	3.80	1.19, 6.60	3.45	1.97, 6.07	2.21	1.11, 4.42
	Neighborhood deprivation (mid versus low)			0.86	0.56, 1.33	0.86	0.55, 1.33
	Neighborhood deprivation (high versus low)			1.51	0.89, 2.55	1.40	0.83, 2.36
	Low parental education			1.11	0.67, 1.85	1.07	0.65, 1.79
	Drug abuse					6.42	3.48, 11.85
1 year	Light smoking versus none	2.15	1.33, 3.48	2.04	1.27, 3.29	1.60	0.97, 2.63
	Heavy smoking versus none	3.44	1.91, 6.20	3.10	1.70, 5.64	1.96	0.95, 4.06
	Neighborhood deprivation (mid versus low)			0.87	0.55, 1.37	0.86	0.55, 1.36
	Neighborhood deprivation (high versus low)			1.59	0.93, 2.71	1.47	0.86, 2.51
	Low parental education			1.11	0.66, 1.87	1.07	0.64, 1.81
	Drug abuse					6.65	3.55, 12.45
3 years	Light smoking versus none	2.16	1.26, 3.68	2.05	1.20, 3.49	1.77	1.02, 3.05
	Heavy smoking versus none	3.58	1.88, 6.80	3.21	1.65, 6.23	2.39	1.09, 5.24
	Neighborhood deprivation (mid versus low)			0.96	0.57, 1.61	0.96	0.57, 1.61
	Neighborhood deprivation (high versus low)			1.89	1.03, 3.48	1.80	0.99, 3.29
	Low parental education			0.90	0.48, 1.69	0.89	0.47, 1.66
	Drug abuse					4.20	1.95, 9.03

[a] Adjustment included both family socioeconomic status (as assessed by low parental education) and community socioeconomic status (as assessed by neighborhood deprivation). Adjustment for drug abuse is based on registration for drug abuse in any of several registries (see the online data supplement).

TABLE 3

Association of Severity of Smoking Habit and Risk for Chronic Obstructive Pulmonary Disease (COPD), Schizophrenia, and Nonaffective Psychosis in Fertile Swedish Women

Category	Reported Smoking Before Pregnancy, at Registration, and at Week 30–32[a]	COPD		Schizophrenia		Nonaffective Psychosis	
		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Reference	(0, 0, 0)						
1	(1–9, 0, 0)	1.45	1.07, 1.97	1.14	0.46, 2.83	1.14	0.85, 1.53
2	(≥10, 0, 0)	1.10	0.69, 1.76	0.86	0.21, 3.52	1.70	1.22, 2.36
3[b]	(+, 1–9, 0) and (+, ≥10, 0)	2.60	1.80, 3.74	0.60	0.08, 4.29	1.70	1.15, 2.49
4	(+, +, 1–9)	4.70	2.85, 5.72	2.58	1.32, 5.05	2.33	1.86, 2.93
5	(+, +, ≥10)	10.83	8.70, 13.47	3.11	1.13, 8.60	2.84	2.01, 4.01

[a] Registration typically occurred at week 12 of pregnancy. "+" indicates any smoking status, and numerals indicate number of cigarettes smoked per day.

[b] Because of the low number of individuals in the (+, ≥10, 0) category, with no cases of schizophrenia among them, it was combined with the (+, 1–9, 0) category.

TABLE 4

Hazard Ratios for Nonaffective Psychosis Per Unit of Cigarette Exposure on a Three-Unit Scale in Full Sisters, Half Sisters, and Cousins Discordant for Smoking and in the Entire Birth Registry Sample[a]

	Full Sisters		Half Sisters		Cousins		All	
Comparison	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
1–9 cigarettes/day versus none	1.48	1.37, 1.59	1.59	1.41, 1.80	1.65	1.55, 1.74	1.64	1.57, 1.71
≥10 cigarettes/day versus none	2.18	1.88, 2.53	2.54	1.98, 3.24	2.71	2.42, 3.04	2.67	2.47, 2.92

[a] In the three-unit scale, one unit equals change from 0 to 1–9 cigarettes/day and from 1–9 to ≥10 cigarettes/day. Thus, hazard ratio for change from 0 to ≥10 cigarettes/day equals the square of the depicted hazard ratio.

TABLE 5

Co-Relative Control Analysis of Hazard Ratios for Nonaffective Psychosis and Chronic Obstructive Pulmonary Disease (COPD) Per Unit of Cigarette Exposure on a Three-Unit Scale[a]

	Monozygotic Twins		Full Sisters		Half Sisters		Cousins	
Disorder and Comparison	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Nonaffective psychosis[b]	(N=3,790)		(N=575,352)		(N=153,938)		(N=1,424,963)	
1–9 cigarettes/day versus none	1.30	1.07, 1.56	1.49	1.38, 1.60	1.59	1.52, 1.66	1.64	1.56, 1.74
≥10 cigarettes/day versus none	1.69	1.17, 2.44	2.21	1.92, 2.55	2.53	2.32, 2.75	2.70	2.42, 3.01
COPD[c]	(N=3,802)		(N=576,878)		(N=154,442)		(N=1,427,178)	
1–9 cigarettes/day versus none	1.71	1.45, 2.00	2.06	1.94, 2.18	2.26	1.7, 2.36	2.37	2.25, 2.51
≥10 cigarettes/day versus none	2.89	2.10, 3.99	4.23	3.76, 4.77	5.12	4.72, 5.55	5.63	5.05, 6.27

[a] In the three-unit scale, one unit equals change from 0 to 1–9 cigarettes/day and from 1–9 to ≥10 cigarettes/day. Thus, the hazard ratio for change from 0 to ≥10 cigarettes/day equals the square of the depicted hazard ratio.

[b] For the model, allowing for a different hazard ratio for each co-relative relationship, we get the following: −2logL=7,842.279 and Akaike information criterion (AIC)=7,850.279. For the model assuming linear dependence, we get the following: −2logL=7,842.743 and AIC=7,846.743. For monozygotic twins, p=0.0053; for all other groups, p<0.0001.

[c] For the model, allowing for a different hazard ratio for each co-relative relationship, we get the following: −2logL=7,330.974 and AIC=7,336.974. For the model assuming the linear dependence, we get the following: −2logL=7,330.974 and AIC=7,334.974. For all groups, p<0.0001.