Schizophrenia Research 212 (2019) 121–125

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Increased risk of smoking-related illnesses in schizophrenia patients: A nationwide cohort study

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ARTICLE INFO

Article history:
Received 5 December 2018
Received in revised form 23 April 2019
Accepted 29 July 2019
Available online 6 August 2019

Keywords:
Schizophrenia
Smoking
Chronic obstructive pulmonary disease
Ischemic heart disease

ABSTRACT

Background: Schizophrenia patients smoke at three times the rate of the general population, and are more susceptible to smoking-related illnesses. The goal of the current study was to evaluate the cumulative probability of chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD) following first documentation of smoking among schizophrenia patients as compared to smoking healthy controls.
Methods: A nationally representative cohort study was designed to assess the odds and cumulative probability of COPD and IHD among individuals with schizophrenia ($n = 10{,}502$) and a matched-sample of smoking healthy controls ($n = 10{,}502$). Hierarchical logistic regressions and Kaplan-Meier regression models were used to compare odds and cumulative probabilities across the two groups.
Results: After adjusting for clinical and demographic factors, smoking schizophrenia patients had a higher probability of receiving a diagnosis of COPD than smoking healthy controls (OR 2.14, 95%CI 1.51 −3.01, $p < 0.001$). The probability of having COPD increased more rapidly in smoking schizophrenia patients, yet the opposite trajectory prevailed for IHD, showing a decreased cumulative probability in smoking schizophrenia patients compared to smoking healthy controls.
Discussion: Schizophrenia has a unique contribution to the facilitation of COPD, which extends beyond the effect of smoking, or other clinical and demographic risk factors. Differential smoking patterns could potentially account for this effect. The differential pattern of IHD should be subjected to further research, as our results might indicate that schizophrenia patients are underdiagnosed with IHD, and may be even less diagnosed as a function of time and chronicity.

1. Introduction

Schizophrenia is associated with increased rates of smoking. Studies indicate that >60% of schizophrenia patients smoke (Dickerson et al., 2018), representing three times the rate of the general population. The high rates of smoking among schizophrenia patients are associated with adverse clinical, financial, and social outcomes, such as more severe mental health symptoms, comorbid substance use, and poorer subjective physical health (Cooper et al., 2012). Smoking also has prominent financial implications for schizophrenia patients who tend to live on fixed public assistance incomes, as the median percentage of income spent by schizophrenia patients on cigarettes is 27.36% per month (Steinberg et al., 2004). Although smoking rates have declined among the general population in developed countries during recent years, no such trend has been observed among psychiatric patients, and studies indicate that fewer than 2% of them are medically treated for tobacco dependence (Montoya et al., 2005). Thus, smoking remains one of the most complex and enduring preventable causes of death and disability in this population.

The higher prevalence of smoking among patients with severe mental illnesses (SMIs) is often regarded as the main contributor of the high premature mortality rate reported in this population (Harker and Cheeseman, 2016). Several studies have reported of an increased risk of death from cardiovascular disease (Lawrence et al., 2013) and cancer (Tran et al., 2009), both of which can be and usually are attributed to smoking. Yet previous studies have also demonstrated strong associations between mental illness and several medical diseases which tended to persist even after adjustment for smoking, such as respiratory disease and

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https://doi.org/10.1016/j.schres.2019.07.058
0920-9964/

cardiovascular disease (Gallagher et al., 2012; Osborn et al., 2007). In Ireland, a cross-sectional study among older adults revealed an association between smoking-related diseases and SMIs, yet smoking did not mediate and rarely moderated this association (Burns et al., 2017). Thus, the role of SMIs in facilitating smoking-related diseases among smoking patients remains to be clarified.

In this study we aimed to clarify the unique role of schizophrenia in facilitating smoking-related illnesses while employing restrictive methodological conditions. Specifically, the objectives of the study were: (a) to assess whether smoking schizophrenia patients have a higher probability of developing chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD) after first documented diagnosis of smoking, compared to smoking healthy controls, and (b) to assess the cumulative probability of being diagnosed with COPD and IHD after first documented smoking among smoking schizophrenia patients as compared to smoking healthy controls. A nationwide cohort study was designed, whereby smoking schizophrenia patients were compared to age and gender frequency-matched smoking healthy controls. In order to maximize control over possible confounders, we adjusted for demographic and medical risk factors.

2. Methods

2.1. Materials and methods

This study was based on nationwide data, derived from the Clalit Health Services (CHS) databases, the largest public managed health care organization in Israel. The study was approved by the institutional review board of Clalit Health Services (Version 001/2015 - November 12, 2015).

2.2. Study population

The CHS is the largest public managed health care organization in Israel, having served a population of about 4,200,000 enrollees in 2013 (Bieber et al., 2013). The diagnoses of chronic diseases are based on real-time input from healthcare providers, pharmacies, medical care facilities, and administrative computerized operating systems. Validation of diagnoses is routinely performed by CHS using logistic checks, such as comparing diagnoses from various sources, and by direct validation of the diagnoses by the treating physicians of each patient. The validity of the diagnoses in the current registry was previously shown to be high (Rennert and Peterburg, 2001).

Patients insured by the CHS and aged 17 to 95 (during the year 2017), with a schizophrenia diagnosis and smoking history, were identified ($n = 10{,}502$) and then paired with age and gender frequency-matched controls ($n = 10{,}502$). The mean age of both groups was 49.66 (SD = 14.38). The control group was randomly sampled at a 1:1 ratio. Patients were defined as having schizophrenia when there was an active schizophrenia diagnosis, as registered by a senior psychiatrist or when listed in the diagnoses of discharge letters from a psychiatric hospital. ICD codes for schizophrenia included all ICD-9 codes for schizophrenia (code 295), including disorganized, catatonic, simple, and paranoid types; acute schizophrenic episode; latent schizophrenia; residual schizophrenia; schizoaffective disorder; and unspecified schizophrenia. Included ICD-10 codes for schizophrenia (code F20) were: paranoid, hebephrenic, catatonic, residual, simple, undifferentiated schizophrenia, and post schizophrenic depression (World Health Organization, 1977, 1992). Identification of smoking was done via the medical documentation registered by a community physician or when listed in the diagnoses of discharge letters from a hospital. Diagnoses in the current cohort were administered from the year 1944 until the year 2017. In order to maintain temporal association, we included only patients who were identified as being smokers prior to the onset of their physical disease (COPD, IHD). The same rule was applied for other medical covariates such as obesity, diabetes mellitus, hypertension, congestive heart failure, cardiomyopathy, and hyperlipidemia.

2.3. Outcomes

Patients were identified as having COPD if they were diagnosed by a physician with an ICD-9 code of 4912 (obstructive chronic bronchitis), 49,120 (obstructive chronic bronchitis without exacerbation), 49,121 (obstructive chronic bronchitis with acute exacerbation), 492 (emphysema), 4920 (emphysematous BLEB), 4928 (other emphysema), 496 (chronic airway obstruction, not elsewhere classified), and 515 (post-inflammatory pulmonary fibrosis). Patients were identified as having IHD if they were diagnosed by a physician with one of the following ICD-9 codes or their sub-categories: 410 (acute myocardial infarction), 411 (other acute and subacute forms of ischemic heart disease), 412 (old myocardial infarction), 413 (angina pectoris), 414 (other forms of chronic ischemic heart disease), 429 (cardiovascular disease, unspecified), V458 (postsurgical aortocoronary bypass status), Z360 (removal of coronary artery obstruction), and Z361 (bypass anastomosis for heart revascularization).

2.4. Covariates

We controlled for baseline demographic characteristics including age, sex, socioeconomic status (SES), sector (general sector, Ultraorthodox Jewish sector, and Arab sector), and marital status (married or unmarried). We added clinical and medical risk factors which were previously reported to be highly prevalent among schizophrenia patients; these included obesity, diabetes mellitus, hypertension, congestive heart failure, cardiomyopathy, hyperlipidemia, alcohol abuse, and drug abuse.

2.5. Statistical analysis

Baseline differences among smoking schizophrenia patients and their matched healthy smoking controls were assessed using the chi-square test for categorical variables and the *t*-test for continuous variables. A hierarchical logistic regression was employed in order to assess the association between schizophrenia and COPD and IHD, while controlling for demographic, clinical, and medical variables. Variables were added to the model in three different blocks (Block 1, demographic variables; Block 2, comorbid medical conditions; Block 3, schizophrenia diagnosis). Estimated projections of the cumulative probability of receiving a diagnosis of COPD and IHD following first documented smoking among individuals with schizophrenia and healthy smoking controls were obtained using the Kaplan-Meier analysis. The log-rank test was used to determine whether survival curves differed statistically between individuals with and without schizophrenia. Statistical analysis was performed using SPSS software, version 25 (SPSS, Chicago, IL, U.S.A.).

3. Results

Among individuals with lifetime smoking, those with schizophrenia were significantly ($p < 0.001$) more likely to be single, belong to the general sector, and have a low socioeconomic status compared to healthy smoking controls. In addition, individuals with schizophrenia were significantly more likely to receive a lifetime diagnosis of obesity ($p < 0.001$), diabetes ($p < 0.001$), congestive heart failure ($p < 0.01$), hyperlipidemia ($p < 0.001$), alcohol abuse ($p < 0.001$), and drug abuse ($p < 0.001$) compared to controls (Table 1). Cumulative consumption of smoking was 14.04 (S.D. = 9.12) among patients with schizophrenia, and 14.30

Table 1
Sociodemographic and clinical characteristics of smoking individuals with a diagnosis of schizophrenia compared to a matched-sample of healthy smoking controls.

	Schizophrenia ($n = 10,502$)		Control ($n = 10,502$)			
	N	%	N	%	χ^2	p-value
Marital status						
Married	2380	22.7	6294	59.9		
Single	8122	87.3	4208	40.1	3008.58	<0.001
Sector						
General	8360	79.6	7926	75.5		
Arab	1660	15.8	2299	21.9		
Ultraorthodox Jews	482	4.6	277	2.6	170.07	<0.001
Socioeconomic status						
Low	4937	47.3	4298	41		
Medium	4171	39.9	4098	39.1		
High	1333	12.8	2087	19.8	207.52	<0.001
Obesity	3259	31	3247	23.2	162.77	<0.001
Diabetes	2435	23.2	1745	16.6	8756	<0.001
Asthma	606	5.8	578	5.5	0.7	0.402
Hypertension	2303	21.9	2341	22.3	0.4	0.527
Congestive heart failure	286	2.7	216	2.1	10	0.002
Hyperlipidemia	5505	52.4	4715	44.9	118.95	<0.001
Drug abuse	859	1.8	192	8.2	445.6	<0.001
Alcohol abuse	425	1.5	155	4	129.25	<0.001

(S.D. = 9.62) among healthy smoking controls ($t = 2.02$, $p = 0.043$). No significant difference was found in age of first documented smoking among individuals with schizophrenia (M = 36.59, S.D. = 15.37) compared to healthy controls (M = 36.26, S.D. = 15.71, $t = 1.542$, $p = 0.12$).

A diagnosis of COPD was observed among 7.4% and 3.2% of individuals with schizophrenia and healthy controls, respectively. Unadjusted univariate logistic regression analysis indicated that individuals with schizophrenia were at a significantly higher risk of developing COPD (OR = 2.41, $p < 0.001$, 95% CI = 2.12–2.75). After controlling for sociodemographic and clinical variables, this association remained, indicating that individuals with schizophrenia had significantly greater odds of developing COPD (adjusted OR = 2.53, $p < 0.001$, 95% CI = 2.23–2.87).

A diagnosis of IHD was observed among 5% and 6.5% of individuals with schizophrenia and healthy controls, respectively. Unadjusted univariate logistic regression analysis indicated that individuals with schizophrenia were at a significantly lower risk of developing IHD (OR = 0.76, $p < 0.001$, 95%CI = 0.67–0.85) compared to healthy controls, yet after controlling for sociodemographic and clinical variables, this association became non-significant (adjusted OR = 0.92, $p = 0.15$, 95% CI = 0.83–1.03), indicating no significant differences in the odds of developing IHD among schizophrenia patients compared to healthy smoking controls (Table 2). An additional sensitivity analysis examining the odds of having a myocardial infarction, which is considered more detectable compared to IHD, also indicated no significant differences in the odds after controlling for sociodemographic and clinical variables (adjusted OR = 0.96. $p = 0.521$, 95% CI = 0.84–1.09).

The mean time between first documented smoking and COPD diagnosis was 11.37 years (S.D = 11.03) among individuals with schizophrenia, and 12.59 years (S.D = 13.9) among healthy controls. A survival analysis (Fig. 1) indicated that beginning at approximately 10 years following first documented smoking, individuals with schizophrenia were at greater odds for COPD diagnosis compared to healthy controls and presented a sharper incline with time in cumulative probability of COPD (log rank test = 181.65, $p < 0.001$). The mean time between first documented smoking and IHD diagnosis was 11.16 years (S.D = 11.47) among individuals with schizophrenia (S.D = 11.03) compared to 13.12 years (S.D = 14.6) among healthy controls. According to the survival analysis, the odds for an IHD diagnosis were slightly higher among healthy controls between 10 and 20 years since first documented smoking, and again at approximately 40 years since documented smoking onward, with a sharper incline with time among healthy controls, peaking at around 60 years following first documented smoking (log rank test = 13.196, $p < 0.001$).

4. Discussion

In this study we assessed the contribution of a schizophrenia diagnosis to the risk of developing a smoking-related illness as compared to smoking healthy controls. After adjusting for demographic and medical comorbid conditions, the findings indicated that schizophrenia patients are at a significantly increased risk of receiving a diagnosis of COPD (OR 2.65), compared to healthy smoking individuals. Inversely, schizophrenia patients were significantly less likely to receive a diagnosis of IHD following smoking as compared to healthy smoking controls (OR 0.88), yet this association was not maintained after controlling for demographic and clinical risk factors. Survival analyses indicated that individuals with schizophrenia receive a diagnosis of COPD more rapidly from the time of their first documented smoking compared to healthy controls, yet a reverse trend was found for a diagnosis of IHD, indicating that smoking control patients received the diagnosis of IHD earlier than individuals with schizophrenia.

Several studies have previously found an increased risk for COPD in patients with schizophrenia. Himelhoch et al. (2004) found that the self-reported prevalence of COPD among adults with SMIs was 22.6%. Using longitudinal administrative claim data, Carney et al. found an increased risk for COPD among schizophrenia patients (Carney et al., 2006). Additional studies conducted in Taiwan

Table 2
Odds ratio and 95% confidence interval of receiving a diagnosis of COPD and IHD, following first documented smoking, comparing individuals with a diagnosis of schizophrenia to a matched-sample of healthy controls.

	Control ($n = 10,502$)	Schizophrenia ($n = 10,502$)	p-Value	Low 95%	High 95%
	OR	OR			
Chronic obstructive pulmonary disease (COPD)					
Model 1[a]	1	2.41	<0.001	2.12	2.75
Model 2[b]	1	2.62	<0.001	2.27	3.02
Model 3[c]	1	2.53	<0.001	2.23	2.87
Ischemic heart disease (IHD)					
Model 1[a]	1	0.76	<0.001	0.67	0.85
Model 2[b]	1	0.96	0.55	0.84	1.1
Model 3[c]	1	0.92	0.156	0.83	1.03

[a] Unadjusted analysis.
[b] Adjustments for sociodemographic variables.
[c] Additional adjustment for additional clinical conditions.

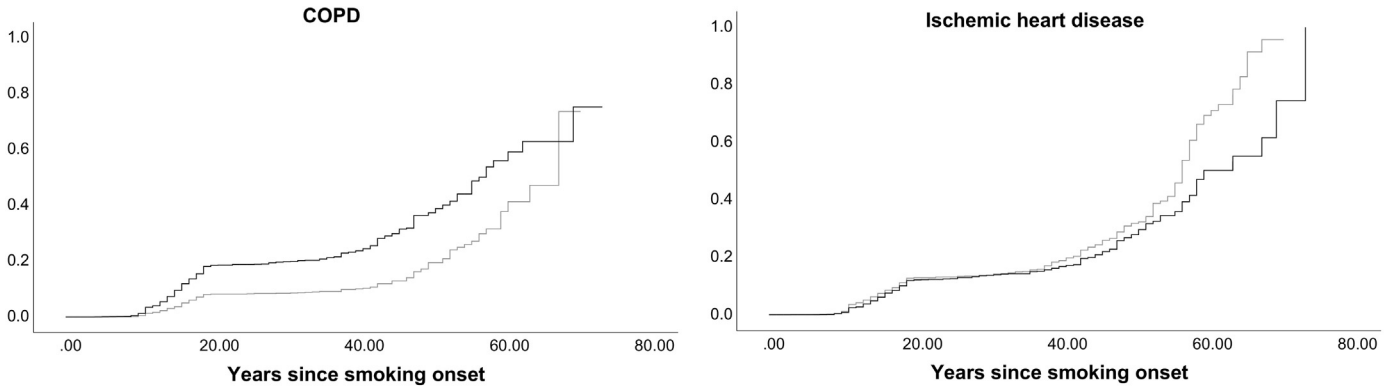

Fig. 1. Cumulative probability of receiving a diagnosis of COPD and IHD among individuals with schizophrenia (black line) and a matched-sample of healthy controls (grey line).

and Denmark also found an increased prevalence of COPD in patients with schizophrenia over that in the general population (Brink et al., 2018; Hsu et al., 2013). A recent systematic review evaluating current literature pertaining to the association between COPD and SMIs reported a greater likelihood of comorbid COPD among schizophrenia and bipolar patients, and concluded that further research is required to ascertain whether smoking is the only cause for this association. Our findings thus indicate that the prevalence of COPD is higher in schizophrenia patients, even after controlling for smoking using a matched sample of smoking controls, and therefore indicate that this higher prevalence cannot be solely attributed to smoking.

The increased risk of COPD, as well as the more rapid onset of the disease among smoking schizophrenia patients can be attributed to differences in smoking patterns. Studies indicate that schizophrenia patients inhale an increased amount of nicotine per cigarette (Williams et al., 2005), have higher rates of nicotine dependence (Jiang et al., 2013; Zhang et al., 2012) and are less likely to engage in smoking cessation programs (Huang et al., 2014). It has been suggested that schizophrenia patients smoke in an effort to restore dopamine blockade caused by certain antipsychotic medications and to diminish their side effects (Williams and Ziedonis, 2004), or else to "self-medicate" for negative psychiatric symptoms such as cognitive impairments (Winterer, 2010). These factors may account for the abnormal smoking patterns among schizophrenia patients which may, in turn, increase the risk for a smoking-related illness and its early onset (also see Aubin et al., 2012). An additional differential smoking pattern that may explain the higher prevalence of COPD in smoking schizophrenia patients is the additional exposure to tobacco smoke caused by passive smoking. Studies indicate that passive smoking is prevalent in mental health facilities, with higher exposure to secondhand smoke in indoor inpatient units (Ballbè et al., 2013). These differential patterns could potentially explain the higher prevalence of COPD among schizophrenia patients compared to smoking controls.

The lower odds of IHD which did not sustain after controlling for risk factors, as well as a slower onset of this disease among smoking schizophrenia patients, warrant additional consideration. One potential hypothesis is that IHD is under-diagnosed in schizophrenia patients. Although schizophrenia patients are known to have elevated mortality rates from IHD, studies fail to demonstrate an increased risk of IHD in schizophrenia, compared to those in the general population (Crump et al., 2013). This diagnostic pattern seems to be unique to IHD, as studies also indicate that women are also diagnosed less frequently with IHD compared to men, but nonetheless present elevated mortality from this disease (Allender et al., 2008; Mikhail, 2005). Studies supporting such a hypothesis indicate that schizophrenia patients are less likely to use general medical services (Cradock-O'Leary et al., 2002), receive less coronary revascularization procedures (Laursen et al., 2009) or antihypertensive and lipid-lowering medication treatment (Lahti et al., 2012), which are crucial in detecting and treating IHD. An additional competing hypothesis is that illness-related factors, such as the use of antipsychotic medications, serve as protective agents against IHD. Previous studies have found a lower risk for IHD in schizophrenia patients using specific types of antipsychotic medications (Daumit et al., 2008), as well as lowered mortality in patients with long-term cumulative exposure to antipsychotic treatment (Tiihonen et al., 2009). This protective trajectory was suggested to be caused by the 5-HT2A receptor blockade, which might protect an individual from IHD and buffer the deleterious metabolic effects of antipsychotics (Blasco-Fontecilla et al., 2010). Nonetheless, the higher prevalence of COPD, as well as the hypothesized pattern of differential consumption patterns, provides more support for the option of an IHD under-diagnosis among these patients, as opposed to the hypothesis of possible illness-related protective factors. These competing hypotheses remain to be examined in future studies.

The current study has several strengths. The comparison of smoking schizophrenia patients to smoking healthy controls allows for an investigation into the contribution of other factors, some of which are smoking-related, to the high prevalence of smoking-related illnesses. The possible impact of smoking habits on the development of COPD might warrant the need to reconsider smoking reduction programs for specific, at-risk, populations such as schizophrenia patients, for the purpose of reducing the risk of developing this disease. The use of a nationally representative large sample, as well as longitudinal approaches, made possible through big data analyses methods, further strengthens the validity of our findings. Nonetheless, the study has several limitations. As the identification of smoking was made by the treating physicians via patients' self-reports, it primarily represents smoking behavior, and not a medical diagnosis, as could have been indicated by an ICD code of nicotine dependence. The current analyses did not control for behavioral factors such as nutrition and level of physical activity, nor for level of nicotine dependence, which could have had an impact on the development of smoking-related illnesses. The use of self-report can potentially cause bias concerning the timing and motives of the reports. Although most epidemiological studies assessing the effect of smoking suffer from this methodological flaw of possible biased self-report, this limitation should be taken under consideration. Taking these limitations into account, the current study indicates that schizophrenia makes a unique contribution to the facilitation of smoking-related illnesses and its rate of onset, possibly through the differential smoking patterns across this population.

Contributors

IK initiated and designed the study, executed and acquired the data, and critically revised the manuscript. DTB performed the literature review, analyzed and interpreted the data, and drafted the manuscript. DC designed the study, collected and organized the data, and critically revised the manuscript. AC initiated and designed the study, acquired the data, and critically revised the manuscript. DF analyzed and interpreted the data, and drafted the manuscript.

Role of funding source

There was no funding source for this research project.

Declaration of Competing Interest

Prof. Arnon Cohen received research grants from Janssen, Novartis, AbbVie, Janssen and Sanofi. Prof. Arnon Cohen served as a consultant, advisor or speaker to AbbVie, Amgen, Boehringer Ingelheim, Dexcel pharma, Janssen, Kamedis, Lilly, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Samsung Bioepis, Sanofi, Sirbal and Taro. All other authors have no conflict of interests to declare.

Acknowledgments

The authors would like to thank Ms. Eve Horowitz Lebobitz for the professional English editing.

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