Association between Alcohol, Cannabis and Other Illicit Substance Abuse and Risk of Developing Schizophrenia: A Nationwide Population Based Register Study

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Abstract

Objective

Several studies have examined whether use of substances can cause schizophrenia. However, due to methodological limitations in the existing literature, like selection bias and lack of adjustment of co-abuse, uncertainties still remain. We aimed to investigate whether substance abuse increases the risk of developing schizophrenia, addressing some of these limitations.

Method

The longitudinal, nationwide Danish registers were linked to establish a cohort of 3,133,968 individuals, identifying 204,505 diagnosed with substance abuse and 21,305 diagnosed with schizophrenia. Information regarding substance abuse was extracted from several registers and did not include psychotic symptoms caused by substance abuse in the definition. This resulted in a large, generalizable sample of exposed individuals. The data was analyzed using Cox regression analyses.

Results

A diagnosis of substance abuse increased the overall risk of developing schizophrenia, hazard ratio (HR), 6.04 (95% confidence interval (CI), 5.84-6.26). Cannabis (HR, 5.20; 95%CI, 4.86-5.57) and alcohol (HR, 3.38; 95%CI, 3.24-3.53) presented the strongest associations. Abuse of hallucinogens (HR, 1.86; 95%CI, 1.43-2.41), sedatives (HR, 1.68; 95%CI, 1.49-1.90), and other substances (HR, 2.85; 95%CI, 2.58-3.15) increased the risk significantly as well. The risk was found to be significant even 10-15 years subsequent to a diagnosis of substance abuse.

Conclusion

Our results illustrate robust associations between almost any type of substance abuse and an increased risk of developing schizophrenia later in life.

Introduction

The role in the development of schizophrenia of an extensive number of genetic and environmental factors has been examined, but a clarification of the pathogenic mechanisms is still needed (1,2). Substance use has been suggested as a potential risk factor (3). Cannabis, stimulants, cocaine and alcohol can cause transient psychosis (4–8). Research suggests a pathophysiological explanation of the psychotic outcome of some of the substances could be increased striatal dopamine level (9–13). A similar neurobiological response is the leading theory of the psychotic symptoms in schizophrenia (14,15). Combined with a high prevalence of substance use among patients with schizophrenia, this has raised the hypothesis of whether they could be a cause of the disorder (16,17).

The hypothesis has been tested in several studies, with cannabis as the dominant focus. The majority of the papers suggests a causal correlation (3,18–20). In the most comprehensive review on the subject, performing meta-analysis the authors found a 40% higher risk of developing psychosis with people who had used cannabis. The authors estimated that if the association was truly causal, 14% of incident cases of psychosis could be prevented if cannabis was not used (3). This is a cause of concern because of the prolonged increase in the incidence rate for cannabis use in Europe (21).

However, several limitations in the existing literature due to study-designs with high risk of selection bias and loss-to-follow up as well as difficulties in reducing the confounding effect of a transient intoxication of a substance has retained the uncertainty of the direction of causation (3,22,23).

We aimed to investigate whether substance abuse can increase the risk of developing schizophrenia, addressing some of the limitations of prior studies, examining the hypothesis with the largest number of participants and types of substances to date.

Methods

The study population consisted of all born in Denmark between January 1, 1955 and December 31, 1999, and was extracted from The Danish Civil Registration System (CRS) which has collected information on the whole Danish population since 1968 (27). Information was extracted from The Danish Psychiatric Central Research Register (PCR) (since 1969), the Danish National Patient Register (NPa), the Danish National Prescription Registry (NPre), the National Alcohol Treatment Register (NAB) and the National Substance Abuse Register (SIB) (24–29). A personal identification number is used in all the national registers, enabling an accurate linkage between the registers. Substance abuse was defined as reported in table 1, and schizophrenia was defined as ICD-8: 295.x, except 295.7 and ICD-10: F20.x. The date of onset of substance abuse and schizophrenia was defined as the date of first contact leading to the diagnoses. Psychotic symptoms caused by substances (ICD-10: 1x.5, 1x.7 and 1x.8) was not included in the definition of substance abuse, as these diagnoses represent a group with a higher vulnerability of developing psychotic disorder. All individuals diagnosed with schizophrenia less than a year after a registration of abuse were classified as non-abuser.

Table 1. Diagnostic Classification of Substance Abuse.

Type of substance abuse	ICD-8 code [I]	ICD-10 code [I]	ATC code [II]	Definition in registers using other classifications than ICD or ATC codes [III]
Alcohol	291, 303, 571.0	F10 (except 10.5, -.7, -.8), E52, G31.2, G62.1, G72.1, K29.2, K86.0, O35.4, Y57.3, Z50.2, Z71.4, Z72.1	N07BB01, N07BB02, N07BB03	Substance abuse was defined as using a substance ≥2-6 times per week or registered as abuser.
Cannabis	304.5	F12 (except 12.5, -.7, -.8)	-	
Cocaine	304.4	F14 (except 14.5, -.7, -.8)	-	
Hallucinogens	304.7	F16 (except 16.5, -.7, -.8)	-	
Opioids	304.0, 304.1	F11 (except 11.5, -.7, -.8)	N07BC01, N07BC51, N07BC02, N07BC03	
Sedatives	304.2. 304.3	F13 (except 13.5, -.7, -.8)	-	
Stimulants	304.6	F15 (except 15.5, -.7, -.8)	-	
Other [IV]	304.8, 304.9	F18 (except 18.5, -.7, -.8) & F19 (except 19.5, -.7, -.8)	-	

[I] Data from PCR and NPa
[II] The Anatomical Therapeutic Chemical Classification System (ATC code). Data from NPr
[III] SIB and NAB do not use ICD or ATC codes
[IV] Other substances: Defined as diagnosis of abuse of other, multiple or unknown psycho-stimulant. Abuses of multiple substances are only diagnosed, when the different abuses are equally serious.

Statistical analyses

The population was followed from birth until diagnosis of schizophrenia, emigration from Denmark, death, or July 1, 2013, whichever came first.

HR (assessments of relative risk) were estimated performing Cox regression analyses using StataMP statistical software, version 13, with substance use disorders as time varying covariates. The p-value and 95% CI were based on likelihood ratio test. We primarily adjusted for other types of substance abuse, to determine the effect of a concurrent substance abuse on the associations. Secondary analyses were additionally adjusted for calendar year (continuous, time-varying variable), gender, urbanicity (born in cities with > 100,000 or <100,000 residents), other non-schizophrenia, non-substance-abuse psychiatric diagnosis (ICD-8: 290 – 315.9 except 291, 295, 303-305 and ICD-10: F00-09, F21-99 except F25, X60-84, Z55-69, Z7 except Z714, Z715, Z717, Z721, Z722, Z77-Z79, Z91 except Z910), parent's psychiatric history (ICD-8: 290 – 315.9 except 303-305 and ICD-10: F00-09, F20-99), parent's history of substance abuse (table 1), parent's country of birth (The World Banks classifications: Denmark, High income, Other (30)) and parent's socioeconomic position (highest educational level, ISCED classification system 1997).

We performed additional analysis for interaction of gender and sensitivity analysis on the population born after 1980 as information on outpatients and emergency room contacts were added in 1995 and by that completing the register.

The identities of the cohort members were blinded to the investigators. The study was approved by the Danish Data Protection Agency.

Results

The cohort of 3,133,968 individuals was followed for 105,178,673 person-years. During follow-up, 21,305 individuals developed schizophrenia (incidence rate (IR): 20.3/100.000 person-years).

Substance abuse was diagnosed in 204,505 persons with 4.627 subsequently developing schizophrenia (IR: 53.7/100.000 person-years). We found no significant difference between the genders in the risk of developing schizophrenia subsequent to a substance abuse (men: HR 6.21; 95%CI, 5.95-6.47, women: HR 5.74; 95%CI, 5.39-6.11) (p-value: interaction of gender: 0.979).

Table 2. Characteristics of the Cohort

Measure	With substance abuse disorder (n=204,505)		Without substance abuse disorder (n=2,929,463)		P-value
Person years	8,612,933		96,565,740		
	N	%	N	%	
Gender					
Male	133,925	65.5%	1,484,915	50.7%	< 0.001
Female	70,580	34.5%	1,444,548	49.3%	
Diagnosed with schizophrenia subsequent to a substance abuse diagnosis					
Yes	4,627	2.3%	16,678	0.6%	< 0.001
No	199,878	97.7%	2,912,785	99.4%	
Age at onset of schizophrenia					
≤ 16	6	0.1%	595	3.6%	< 0.001
17-25	1,307	28.2%	8,167	49.0%	
25-30	1,019	22.0%	3,194	19.2%	
30-35	817	17.7%	2,084	12.5%	
>35	1,478	31.9%	2,638	15.8%	
Urbanicity at birth [11]					
< 100.000 residents	134,952	66.0%	1,949,654	66.6%	< 0.001
> 100.000 residents	69,392	33.9%	876,827	29.9%	
Unknown	161	0.1%	102,982	3.5%	
Any psychiatric diagnosis other than diagnosis of schizophrenia and substance abuse					
Yes	17,338	8.5%	237,265	8.1%	< 0.001
No	187,167	91.5%	2,692,198	91.9%	
Mother diagnosed with psychiatric disorder other than substance abuse					
Yes	36,387	17.8%	312,011	10.7%	< 0.001
No	168,118	82.2%	2,617,452	89.3%	
Father diagnosed with psychiatric disorder other than substance abuse					
Yes	25,456	12.4%	228,508	7.8%	< 0.001
No	179,049	87.6%	2,700,955	92.2%	
Mother diagnosed with substance abuse					
Yes	28,970	14.2%	183,477	6.3%	< 0.001
No	175,535	85.8%	2,745,986	93.7%	
Father diagnosed with substance abuse					
Yes	41,708	20.4%	308,995	10.5%	< 0.001
No	162,797	79.6%	2,620,468	89.5%	
Mother's country of origin					
Denmark	190,336	93.1%	2,624,625	89.6%	< 0.001
High income	5,386	2.6%	96,791	3.3%	
Other level income	2,681	1.3%	85,753	2.9%	
Unknown	6,102	3.0%	122,294	4.2%	
Father's country of origin					

Denmark	185,348	90.6%	2,589,931	88.4%	< 0.001
High income	4,263	2.1%	81,031	2.8%	
Other level income	3,620	1.8%	97,060	3.3%	
Unknown	11,274	5.5%	161,441	5.5%	
Mother's educational level					
Primary	309	0.2%	10,394	0.4%	< 0.001
Lower secondary	105,772	51.7%	1,051,868	35.9%	
Upper secondary	58,087	28.4%	992,613	33.9%	
Post-secondary	7	0.003%	294	0.01%	
First stage of tertiary	26,282	12.9%	651,261	22.2%	
Second stage of tertiary - advanced research qualification	113	0.1%	5,174	0.2%	
Unknown	13,935	6.8%	217,859	7.4%	
Father's educational level					
Primary	181	0.1%	5,519	0.2%	< 0.001
Lower secondary	76,993	37.6%	812,687	27.7%	
Upper secondary	74,813	36.6%	1,179,755	40.3%	
Post-secondary	38	0.02%	819	0.03%	
First stage of tertiary	23,544	11.5%	581,286	19.8%	
Second stage of tertiary - advanced research qualification	195	0.1%	10,000	0.3%	
Unknown	28,741	14.1%	339,397	11.6%	

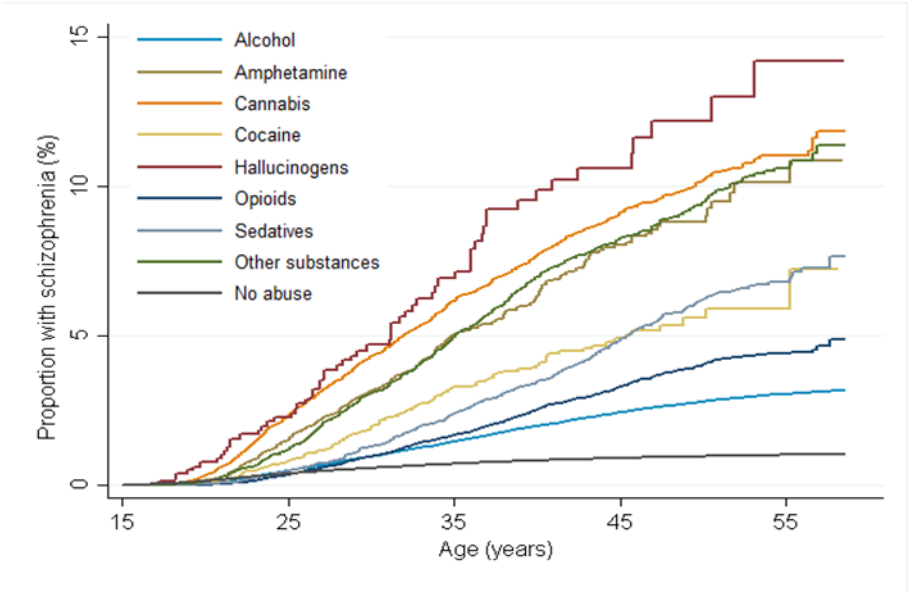
[I] The overall p-value for the group comparison assessed using the Chi squared test.
[II] Contains only information from 1980. Individuals born before 1980: classified as 1980 information. Death before 1980 or no registered place of birth: unknown status of urbanicity.

A positive history of substance abuse increased the overall risk of developing schizophrenia relative to not abusing (HR 8.83; 95%CI, 8.54-9.13). Unadjusted, the highest associations were found with abuse of hallucinogens (HR 22.91; 95%CI, 17.82-29.46) and cannabis (HR 22.67; 95%CI, 21.48-23.92). After adjusting for other types of substance abuse, strong associations remained between abuse of cannabis (HR, 7.52; 95%CI, 7.00-8.07), alcohol (HR, 4.51; 95%CI, 4.31-4.71) and other substances (HR, 2.62; 95%CI, 2.28-2.90). Abuse of hallucinogens, sedatives, stimulants or opioids was only weakly, but significantly, associated with schizophrenia. Cocaine abuse alone presented no longer any significant association. Additional adjustment for calendar year, gender, urbanicity, any psychiatric diagnosis prior to substance abuse, parent's psychiatric history, parent's history of substance abuse, parent's immigration to Denmark and parent's socioeconomic position did not greatly affect the results further. Only cocaine-abuse was negatively associated after the complete

adjustments were made (HR, 0.70; 95%CI, 0.58-0.83). Limiting the cohort to only including individuals born after 1980 resulted in a risk of HR, 3.95 (95%CI, 3.68-4.23).

Kaplan Meier curves illustrates the proportion of incident diagnosis of schizophrenia (figure 1). Figure 2 illustrates the risk of being diagnosed with schizophrenia was strongest within a year after diagnosed with substance abuse. The risk decreased in the subsequent years, but remained significant even after 10-15 years.

Figure 1: Risk of Schizophrenia for All Substance Abuse Disorders



Discussion

We found, an association between almost any kind of substance abuse and schizophrenia, with abuse of cannabis and alcohol presenting the highest risks. After all adjustments were made the HR were reduced however still significant for almost all types of substances. The risk of developing schizophrenia was significantly increased even 10-15 years subsequent a substance abuse. We found in general stronger associations compared with estimates reported in other studies (3,5,20). However, this could be explained by our investigation of substance abuse in comparison to previous studies examining the association with substance use on a broader scale, as previous papers on cannabis use have found statistical evidence in favour of a dose-response relationship (3). One other study investigated substance abuse as a risk factor, and found in general higher associations compared with

the present study (19). However, a lack of adjustment for other types of substances could overestimated these results. We found, that the attenuation of the HR between the unadjusted and fully adjusted results was largely caused by the effect of a poly-drug abuse, which brings new information to the area (data not reported). Conversely, the adjustment could also cause an over-adjustment, illustrated by the finding of a negative association with cocaine, as the crude results highly indicate the reverse association.

Table 3. Risk of Schizophrenia for All Substance Abuse Disorders

Type of substance abuse		No. of persons at risk during follow-up	No. of new cases during follow-up	Unadjusted		Adjustment 1 [I]		Adjustment 2 [III]	
				HR	95% CI	HR	95% CI	HR	95% CI
No abuse		2,929,463	16,678	1	[Ref.]	1	[Ref.]	-	-
Any abuse		204,505	4,627	8.83	8.54-9.13	6.04 [II]	5.84-6.26	-	-
Total		3,133,968	21,305		-		-		-
Alcohol									
	No abuse	2,973,632	18,080	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	160,336	3,225	6.84	6.58-7.10	4.51	4.31-4.71	3.38	3.24-3.53
Cannabis									
	No abuse	3,111,105	19,857	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	22,863	1,448	22.67	21.48-23.92	7.52	7.00-8.07	5.20	4.86-5.57
Cocaine									
	No abuse	3,129,422	21,159	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	4,546	146	13.03	11.08-15.31	0.84	0.71-1.01	0.70	0.58-0.83
Hallucinogens									
	No abuse	3,133,208	21,244	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	760	61	22.91	17.82-29.46	1.62	1.25-2.11	1.86	1.43-2.41
Opioids									
	No abuse	3,113,698	20,701	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	20,270	604	10.71	9.87-11.63	1.15	1.04-1.28	1.20	1.08-1.32
Sedatives									
	No abuse	3,126,116	20,938	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	7,852	367	18.70	16.86-20.74	1.57	1.39-1.78	1.68	1.49-1.90
Stimulant									
	No abuse	3,127,535	20,989	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	6,433	316	16.08	14.36-18.00	1.22	1.08-1.39	1.24	1.09-1.41
Other									
	No abuse	3,126,197	20,761	1	[Ref.]	1	[Ref.]	1	[Ref.]
	Abuse	7,771	544	16.13	14.81-17.58	2.62	2.28-2.90	2.85	2.58-3.15

[I] Adjusted for other type of substance abuse
[II] Adjusted for calendar year, gender, urbanity, any psychiatric diagnosis prior to substance abuse, parent's psychiatric history, parent's history of substance abuse, parent's immigration to Denmark and parent's socioeconomic position
[III] Adjusted for other type of substance abuse, calendar year, gender, urbanity, any psychiatric diagnosis prior to substance abuse, parent's psychiatric history, parent's history of substance abuse, parent's immigration to Denmark and parent's socioeconomic position

The tendency of a more intensive and regular use of substances reported with men, as well as men's increased risk of developing schizophrenia in general, could have resulted in higher risk compared

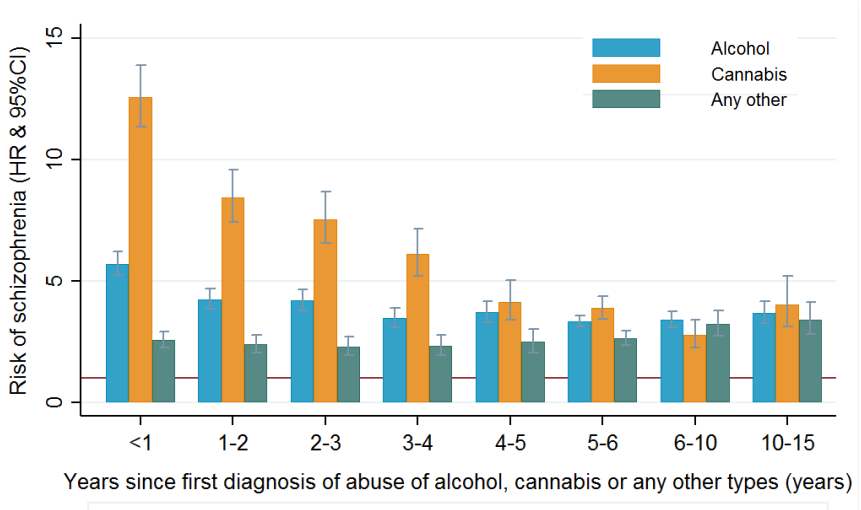
with women (21,31,32). However, we observed no significant difference in the risk of developing schizophrenia subsequent to a substance abuse between the genders.

The lower HR found in the sensitivity analysis of the 1980-population could be explained by the markedly lower number of cases (5.857 cases). Conversely, the result could be closer to the true measure of association, as it is based on a more complete psychiatric information.

The strengths of the study are the longitudinal, prospective design based on the nationwide Danish registers, ensuring a large study population and a high number of cases with a minimum of loss-to-follow up and recall bias effects (24,28). Extracting information from several registers increased the number of registered abusers, however, an underestimation of the diagnosis of substance abuse must be anticipated. The sparse data on the psychological development from birth from the registers on this area is a study limitation as well.

The rule of classifying any diagnosed with schizophrenia less than a year after a substance abuse as non-abuser is conservative. However, the rule addressed the effects of the disorders developing in an individual length of time prior to the registration in the registers as well as detection bias caused by a hospital contact for schizophrenia possibly entailing a subsequent risk of being diagnosed with a substance abuse (figure 2).

Figure 2: Time since diagnosis of Abuse of Substances and Risk of Developing Schizophrenia



Any other substance: pooled group of stimulants, cocaine, hallucinogens, opioids, sedatives and other.
The HR are adjusted as reported in adjustment 2, table 3.

Other confounders could have affected the results as well (34,35).

In conclusion, the consumption of substances is an extensive problem throughout the world and a current debate on legalizing cannabis in many countries has made uncovering the risk of abusing substances an important area of investigation (21,36). We found robust associations between a wide variety of substance abuse and an increased risk of developing schizophrenia. We are not aware of any other study focusing on the effect of such a wide variety of substance abuse and the interaction between the abuses as our study.

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