Use of alcohol, drugs, inhalants, and smoking tobacco and the long-term risk of depression in men: A nationwide Swedish cohort study from 1969-2017

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Abstract

Background: The use of alcohol, drugs, inhalants, and smoking tobacco may lead to mood disorders such as depression. However, knowledge on the independent contributions of the use of these substances to the risk of depression is lacking.

Methods: The study cohort consisted of 24,564 men included in the Swedish national military conscription register who were conscripted in 1969–1970 and followed until 2017. Cox proportional hazard ratios were used to estimate the risk of depression according to alcohol, drug, inhalant, and cigarette consumption, and adjusted for body mass index, verbal comprehension test scores, handgrip strength, and the other main exposures investigated.

Results: During an average follow-up period of 44 years, 4500 men were diagnosed with or treated for depression at a mean age of 54 years. A dose-dependent association was found in men who smoked cigarettes, with the highest risk for smoking >20 cigarettes per day, at time of conscription (aHR 1.86, 95% CI 1.61–2.16, $p < 0.001$). Independent associations with an increased risk of depression were found for the use of drugs at least once (aHR 1.21, 95% CI 1.10–1.32, $p < 0.001$) and >50 times (aHR 1.48, 95% CI 1.23–1.77, $p < 0.001$) and the use of inhalants (aHR 1.16, 95% CI 1.05–1.29). Excessive alcohol intake was not associated with the risk of depression.

Conclusion: The results suggest that people who reported to have used cigarettes, alcohol, or drugs at 18 years of age have a moderately increased risk of depression later in life.

Keywords: Alcohol Disorder, Drug Abuse, Depression, Smoking;

1. INTRODUCTION

Depression is a disease affecting about 350 million people worldwide and the leading cause of disability, especially among women (Marcus et al., 2012). Various preventive programs have been used in public health care to reduce its incidence and consequences. Generally, these programs are based on community approaches that aim to strengthen protective factors and reduce risk factors. Previously identified potential risk factors include the use of tobacco, alcohol, inhalants, and drugs, which may influence mood regulation (Boden and Fergusson, 2011; Caldwell et al., 2002; Jane-Llopis et al., 2006).

Recent researches have confirmed the association between smoking habit and the risk of depression (Boden et al., 2010; Klungsøyr et al., 2006; Pasco et al., 2008; Wootton et al., 2018). In one study (Pasco et al., 2008), smoking exposure was associated with an increase of about 50% in the risk of major depressive disorder. Moreover, the risk of *de novo* depression development tended to double over 10 years among smokers, independently from age and alcohol consumption.

In a meta-analysis, Boden and Fergusson (2011) found that the risk of major depressive disorder was doubled in people with alcohol abuse disorder, while findings about wine are not consistent, since moderate wine consumption was associated with a lower risk of depression (Gea et al., 2013). Nevertheless, a cohort study showed that the best predictor of this relationship is the frequency of hangovers, which indicates a frequent alcohol abuse (Paljärvi et al., 2009).

Wu and Howard (2007) reported that 35% of inhalant users aged ≥ 18 years displayed major depressive disorder, that was later confirmed by Perron and Howard (2009), who showed that 40% of inhalant users had major depressive disorder. Less is known about whether these cross-sectional associations would be sustained in longitudinal studies. Finally, chronic drug consumption may lead to neurobiological changes that increase the risk of developing depression later in life (Volkow, 2004), and a meta-analysis confirmed this risk in young adulthood (Gobbi et al., 2019).

However, these mainly cross-sectional studies have not demonstrated clearly whether the intake of these substances causes depressive symptoms, if it serves as "self-medication" to reduce emotional distress in cases of depression, or if smoking and depression both depend on genetic factors and are likely to emerge at different stages of life (Markou et al., 1998; Pasco et al., 2008; Wootton et al., 2018).

The studies investigating these associations adopted cross-sectional designs, small cohorts, and/or short follow-up periods, which may increase the risk of reverse causality. No previous cohort studies have examined the existence of independent associations between the use of different substances in young age and the risk of depression later in life. The aim of this nationwide study is to fill this gap in literature. Therefore, we hypothesize that the use of tobacco, alcohol, inhalants, and drugs in young age would be independently associated with a greater risk of developing depression later in life.

2. METHODS

2.1 Participants

This cohort study was conducted using the Swedish national military conscription register, which contains data on 24,564 Swedish men born between 1950 and 1954, including date of conscription. Most (99.5%) included participants were conscripted in 1969–1970, and the follow-up period extended to December 31, 2016. Individuals who died before the diagnosis of depression or the end of the study period were censored. Also, conscripts who were diagnosed for depression before the conscription date were excluded as well. This study was conducted according to the STROBE statement (Vandenbroucke et al., 2007).

2.2 Outcome

The outcome of interest in the present study was depression. The study used Swedish National Patient Register (NPR), managed by the National Board of Health and Welfare, which gave the ethical approval for the study. The diagnoses of depression were identified by International Classification of Diseases codes 296 (versions 8 and 9) and F32 and F33 (version 10). About 90% of diagnoses made during inpatient care is recorded in NPR since 1976, complete since 1987, and all diagnoses in outpatient specialist care are since 2001 recorded in the NPR. These diagnoses have about 90% positive predictive value (Ludvigsson et al., 2011). The outcome was also assessed based on NPR records of the dispensation of drugs used to treat depression, including those bearing the Anatomical Therapeutic Chemical (ATC) Classification System code N06A (antidepressants). The NPR contains data on all drugs prescribed and dispensed outside of hospitals in Sweden since 2005.

2.3 Main exposures

The main exposures examined in the present study were tobacco smoking, drug use, inhalant use, and alcohol consumption at the time of conscription. In 1969 and 1970, a questionnaire was administered to conscripts and included questions regarding these exposures. The item used to assess tobacco smoking was “How much do you smoke per day?” (response options: “do not smoke,” “1–5 cigarettes/day,” “6–10 cigarettes/day,” “11–20 cigarettes/day,” and “>20 cigarettes/day”). A sample item for assessing drug use was “Have you ever used drugs?” (“yes”/ “no”), and the possible drugs presented in a later question (“Which drug have you used most often?”) were “cannabis/hashish”, “ritalin”, “amphetamine”, “morphine”, “LSD”, “opium”, “nembutal”, “restenil”, and “other drugs”, although this question was not included in the subsequent analyses. For assessing inhalant use was “Have you ever sniffed varnish or similar?” (response options: “never,” “once,” “2–10 times,” and “>10 times”), and for alcohol consumption was “how

often do you usually drink beer?" (response options: "almost daily", "sometimes in a week", "rarely", "never"). The complete list can be found in the tables 2 and 3.

2.4 Confounders

Body mass index (BMI), handgrip strength, and verbal comprehension were included in the current study as potential confounders. These variables were collected at the time of conscription. BMI was obtained by dividing each subject's weight (in kilograms) by his squared height (in meters) (Organization, 2000). It was considered to be a potential confounder since obesity is notably associated with the risk of developing depression, compared to non-obese group (Dong et al., 2004). Moreover, people with higher BMI tend also to be sedentary, smoke more, and consume more alcohol (Daw et al., 2017). As BMI data were not distributed normally, measures were divided into quartiles.

A verbal comprehension test was administered to the study subjects as one of four cognitive function tests from the Swedish enlistment battery (Carlsted and Mårdberg, 1993; Carlstedt, 2000), which is based on the theoretical model of intelligence presented by Gustafsson (Gustafsson, 1988a, b). The test consists of 40 items of increasing difficulty. Each item contains a target word for which the individual must choose the correct synonym among four alternatives. Each correct answer earns one point, resulting in a maximum score of 40 points. Verbal comprehension could act as confounder since it is an indicator of educational attainment, which is, in turn, associated with socioeconomic status, that is a predictor of depression (Huurre et al., 2007; Mezuk et al., 2008).

Handgrip strength (in Newtons, N) was assessed using a handgrip dynamometer. Each conscript was asked to squeeze the grip as tightly as possible with his dominant hand while standing with the elbow in 90° flexion. The strongest grip among three replicates was recorded; when the last repetition yielded the highest value, the test was repeated. This variable was considered to be a potential confounder because muscular strength is an indicator of physical fitness, which is, in turn,

associated with the risk of depression (Pasco et al., 2008). For the statistical analysis, grip strength values were divided into quartiles.

2.5 Data analysis

Data were analyzed using IBM SPSS 23.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were calculated for age, height, weight, BMI, verbal comprehension, and handgrip strength, and ANOVA was used to compare differences among depressed and non-depressed respondents. Follow-up periods were estimated by calculating the difference between the conscription date and the first diagnosis of depression, death, or December 31, 2016 (whichever came first). Cox regression models were used to examine associations of the exposure variables with the outcome of depression. The main exposures (number of cigarettes smoked per day; frequencies and quantities of beer, wine, and liquor consumption; frequency of hangover; drug and inhalant use [yes/no] and if yes numbers of times) were examined as predictors of the risk of depression. Three models were used: the first model was unadjusted; the second model was adjusted for BMI, verbal comprehension, and handgrip strength; and the third model was adjusted additionally for the use of other substances. The proportional hazard assumption for the Cox regression models was tested using log-log plots. Since conscripts could have not been honest in their answers, sensitivity analyses were performed to assess the validity of the questionnaire used during conscription and the prediction of outcomes that are frequently associated with the exposures. Specifically, the associations of the number of cigarettes smoked with the subsequent diagnosis of chronic pulmonary disease, the amount of alcohol consumed with the risk of later alcohol intoxication, and inhalant and drug use with the subsequent risk of substance intoxication diagnosis were tested. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated, and p values < 0.05 were considered to be significant.

3. RESULTS

3.1. Sample characteristics

The subjects' characteristics are summarized in Tables 1 and 2. At the time of conscription, the mean age of the 24,564 men was 18.1 (standard deviation [SD] 0.5) years and the average BMI was 20.9 (SD 2.6) kg/m^2. The average verbal comprehension test score was 22.3 (SD 6.5) and the mean hand grip strength was 601.1 (SD 97) N (Newton).

Individuals with depression during the follow-up period had lower verbal comprehension test scores (mean difference –0.73, $p < 0.001$) and lesser handgrip strength (mean difference –3.72 N, $p = 0.02$) than did the rest of the cohort. At the time of conscription, 59.4% of the men reported smoking, 92.2% reported drinking at least one glass of beer on each occasion, 79.6% reported drinking at least one glass of wine on each occasion, and 76.3% reported drinking liquor. In addition, 14.3% of conscripts reported using inhalants at least once, 12.2% reported trying drugs at least once, and 9.5% reported the desire to use drugs. Of those who had tried drugs, 79.1% reported that the first drug they tried was cannabis. Significant differences between depressed and non-depressed individuals were found for the number of cigarettes smoked per day, frequencies of beer and wine consumption, quantity of beer usually consumed, frequency of hangover, inhalant and drug use, frequency of drug use, and desire to use drugs (all $p < 0.05$).

INSERT TABLE 1 HERE

INSERT TABLE 2 HERE

3.2 Risk of depression

As the proportional hazard assumption was not violated, associations were examined using unconditional Cox regression models. The main results of the analysis are presented in Table 3 and Figure 1.

During an average follow-up period of 44 years, 4500 men were diagnosed with or treated with depression for the first time, at a mean age of 54 years. Smoking increased the risk of depression in a dose-dependent manner, and this relationship was stable across the three statistical models. With non-smokers serving as the reference group, the final model revealed an increased risk of depression during a mean follow-up for those smoking 1–5 cigarettes (adjusted hazard ratio [aHR] 1.21, 95% CI 1.09–1.34, $p < 0.001$), 6–10 cigarettes (aHR 1.28, 95% CI 1.18–1.39, $p < 0.001$), 11–20 cigarettes (aHR 1.40, 95% CI 1.29–1.52, $p < 0.001$), and >20 cigarettes (aHR 1.86, 95% CI 1.61–2.16, $p < 0.001$) per day.

Individuals who drank beer every day were at risk of depression in the unadjusted model (HR 1.36, 95% CI 1.27–1.58, $p < 0.001$), but not in the model adjusted for confounders and for smoking and drug consumption (aHR= 1.09, 95% CI 0.93; 1.28, *ns*). Similar results were obtained for individuals who drank more than three glasses of beer on each occasion (aHR 0.97, 95% CI, 0.85; 1.10, *ns*), drinking wine every day (aHR= 0.87, 95% CI 0.33; 2.32, *ns*), drank more than one bottle of wine on each occasion (aHR= 1.01, 95% CI 0.88; 1.17, *ns*), and drank more than 35 cl liquor on each occasion (aHR= 0.97, 95% CI 0.85; 1.11, *ns*). In contrast, individuals who often experienced hangover had a greater risk of developing depression than non-drinkers, as determined by the model adjusted for other exposure factors (aHR 1.21, 95% CI 1.02–1.42, $p = 0.02$).

Inhalant use was associated with the risk of depression in the unadjusted model (HR 1.32, 95% CI 1.07–1.62, $p = 0.009$), and in the model adjusted for confounders including cigarette and alcohol consumption (aHR 1.16, 95% CI 1.05–1.29, $p = 0.004$). The model adjusted for all confounders revealed that individuals who had taken drugs at least once had a greater risk of depression (aHR 1.21, 95% CI 1.10–1.32, $p < 0.001$) compared to non-users; similar results were obtained for individuals who had used drugs more than 50 times (aHR 1.48, 95% CI 1.23–1.77, $p < 0.001$).

INSERT TABLE 3 HERE

INSERT FIGURE 1 HERE

3.3 Sensitivity analysis results

The results of the sensitivity analysis are presented in Table 4. Compared with not smoking at the time of conscription, smoking more than 20 cigarettes a day increased the risk of chronic obstructive pulmonary disease during follow up by about 20 times (aHR= 19.21, 95% CI 12.96–28.49, $p < 0.001$). Individuals who drank beer every day had about six times the risk of alcohol intoxication during follow up compared to non-drinkers (aHR= 5.88, 95% CI 3.35–10.33, $p < 0.001$). The frequency of wine consumption increased the risk of alcohol intoxication (aHR= 5.03, 95% CI 2.38–10.67, $p < 0.001$), as did the quantity of liquor consumed on each occasion (aHR= 3.38, 95% CI 2.77–4.12, $p < 0.001$) compared to non-drinkers. Drug intoxication was related to the use of inhalants (aHR= 7.48, 95% CI 5.66–9.88, $p < 0.001$) and drugs (aHR= 11.55, 95% CI 9.21–14.48, $p<0.001$), as well as the frequent desire to use drugs (aHR= 6.36, 95% CI 3.48–11.60, $p<0.001$) compared to those who never used these substances.

INSERT TABLE 4 HERE

4. DISCUSSION

The current study aimed to evaluate independent associations between the use of tobacco, alcoholic beverages (beer, wine, liquor), inhalants, and drugs in early adulthood and the risk of depression later in life. It revealed a dose-dependent relationship between smoking and depression, with the smoking of more than 20 cigarettes per day at the time of conscription approximately doubling the risk of subsequent depression. In addition, drug use was associated independently with an increased risk of depression, and the use of drugs more than 50 times by the time of conscription had about 50% increased risk. In contrast to the findings of most previous studies, the amount of alcohol consumed was not associated independently with the risk of depression later in life.

About 65% of the men in the cohort that used tobacco at the time of conscription developed depression later in life. These findings indicate that smoking habits constitute an especially important risk factor for depression diagnosis or antidepressant use in the long term. Specifically, nicotine may alter the neurotransmitter regulation, including dopamine, via the already known cholinergic pathways, and this could have a significant role in mood disorder development (Dani and De Biasi, 2001).

A novel finding of this study is that the association between tobacco use and depression was independent of the use of other substances, such as alcohol and drugs. This result stands in contrast to the one from another study, where the use of cigarettes at age of 16 years was associated to an increased odds of depression at age of 18, but after adjusting for cannabis use, the relation between depression and cigarette use disappeared (Gage et al., 2015). This lack of association could also be explained by lower statistical power, as the researchers had complete data for only 1791 of 4561 individuals.

Results from the few previous studies of associations between drug use and the risk of developing depression later in life are not consistent, at least when cannabis use is included (Gage et al., 2015; Grant, 1995). Wu and Howard (2007) and Perron and Howard (2009) reported associations between inhalant use and depressive symptoms; the association with inhalants identified in this study was rather weak. Regardless, drug and inhalant use clearly has a smaller impact than smoking on the subsequent risk of depression at the community level, given that it is much more uncommon (Gage et al., 2015). Less than 15% of our cohort reported that they had used drugs or inhalants at the time of conscription.

In contrast to drug and inhalant use, the use of alcohol could have a major impact on depression, given that it is common in society. More than 90% of the men in our cohort consumed alcohol at the time of conscription. Many aspects of alcohol use were associated with the risk of depression later in life in our unadjusted analysis. However, after adjustment for concomitant exposures, including smoking, only frequent hangover remained associated independently with the

risk of depression. These results suggest that alcohol intake per se has no major impact on the risk of depression. Previous research has yielded inconsistent results regarding the relationship between alcohol intake and the risk of depression (Bulloch et al., 2012; García-Esquinas et al., 2018; Haynes et al., 2005; Wang and Patten, 2001). Based on the results of our study, one important explanation for this inconsistency might be the lack of adjustment for other exposures, especially smoking habit.

Some limitations of the present study should be considered. First, the observational design limited our ability to make causal inferences. Moreover, the cohort consisted exclusively of men. Thus, the results should be generalized only to other male populations, and future cohort studies should investigate gender differences in these relationships. Also, the outcome of depression was assessed including the prescription of antidepressant, which are mainly used for depression, but also for other conditions which might result in misclassification of depression. Another limitation consists of lack of information about socioeconomic status at conscription, which is known to be associated with drinking and smoking habits.

The main problem associated with research on factors such as alcohol and substance use is the validity of subjects' responses (Krumpal, 2013). Data on the considered exposures were collected only once, and subjects' exposures likely changed during the follow-up period, for example they could have changed drug or have stopped using them. For these reasons, we evaluated the validity of the data using sensitivity analyses and confirmed that reported substance use was associated with relevant outcomes, suggesting that the questionnaire used elicited valid responses. If the respondents misrepresented their smoking-, alcohol-, and drug-related behavior, the associations found in this study should likely have been stronger. It should also be emphasized that any changes in the main exposures during follow up, missed diagnoses in the registers used in the present study, or misclassification of depression, would likely attenuate the associations found. Strengths of the study lude the examination of a large cohort with 4500 outcomes and a follow-up period of almost 50 years.

5. CONCLUSION

In summary, the findings of the present study suggest that smoking in young adulthood is moderately associated with the risk of depression later in life among men. The use of drugs and inhalants was also associated independently with the risk of depression, although the societal impact of such substance use is smaller, given its lower prevalence. Within the limitations of this observational study, the findings suggest that people who reported to have used cigarettes, alcohol, or drugs at 18 years of age have a moderately increased risk of depression later in life. These results contribute to strengthen the existing literature on the damaging effects of substances abuse, also considering the public health impacts of depression and depressive symptoms.

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Figure 1 – Forest plot for the main exposures