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► To cite this version:

Joane Matta, Nicolas Hoertel, Guillaume Airagnes, Emmanuel Wiernik, Frédéric Limosin, et al.. Does substance use explain social differences in terms of depression? Findings from the Constances cohort. *Comprehensive Psychiatry*, 2020, 102, pp.152203 -. 10.1016/j.comppsy.2020.152203 . hal-03492293

HAL Id: hal-03492293

<https://hal.science/hal-03492293v1>

Submitted on 14 Sep 2022

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Title: Does substance use explain social differences in terms of depression? Findings from the Constances cohort

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Running title: Substance use, social inequality, and depression

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1. Abstract

Background: The role of alcohol, tobacco and cannabis use in social differences in terms of depression is poorly understood.

Methods: We have applied mediation and moderated-mediation models stratified by gender to a population-based sample (N=37,192) of French men and women from the Constances cohort with baseline and follow-up measures of depressive states. We have examined whether socioeconomic status (SES, measured by education and income) differences in the prevalence of depressive states may be explained by both differences in prevalence of substance use according to SES (mediating effects) and differential effects of substance use on depressive state according to SES (moderating effects).

Results: In the mediation models, substance use only explained 5.3% and 2.4% of the association between low education and depressive state in men and women respectively, and was not a significant mediator for income. Moderated mediation models showed robust moderation effects of education and income in both men and women. The association of tobacco use with depressive symptoms, which was the only substance for which a mediation effect remained and for which the moderation effect of SES was the strongest, was significantly higher in participants with low SES.

Limitations: The partially cross-sectional nature of the data restricts the possibility of drawing causality with regards to associations between SES and substance use.

Conclusion: Targeting substance use, particularly tobacco, can especially reduce depression risk in individuals of low SES.

Keywords: Depression; social differences; substance use.

2. Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide. As for many other psychiatric and somatic conditions, there is growing evidence of the contribution of social inequalities in the risk of MDD(1). Specifically, these studies show that indicators of low SES, either as composite or discrete scores, such as low education level or low income, are associated with greater risk of MDD, in both cross-sectional(2) and longitudinal studies(3, 4). Regarding the association with low education, it has been found in both men and women(5) and in both low-income(6) and high-income countries(5); additionally it may be independent of individual or household income(2). A meta-analysis of 37 studies mainly from Western countries has found a three per cent decrease in log odds ratio for depression per additional year of education(2). Moreover, income has been shown to be an independent predictor of depression(7, 8) and to partially mediate the association between education and depression(5).

Several explanations may account for these social inequalities in the risk of MDD. It has been shown that inequalities are associated with increased psychological stress(9). For instance, low income may increase loneliness and isolation(10), and limits access to healthcare and housing, which consequently may increase the risk of developing psychiatric disorders including MDD(11). Although material factors, specifically financial strain, may have higher mediating than psychosocial function in this association(12), as the act of comparing oneself to someone else with more favorable social position may create a feeling of social defeat that in turn leads to depression(13). However, the role of substance use in either mediating or moderating the association between low SES and depression remains understudied.

Low educational attainment had been associated with a higher risk of non-problematic heavy drinking and problematic drinking(14). Moreover, those individuals with a lower socioeconomic background bear more burden of alcohol-related harm(15). Regarding tobacco use, people with

low SES tend to smoke more frequently(16) and have a harder time quitting consumption. The same pattern has been observed with cannabis use(17). The association between substance use and low income/education status may occur because of a relative lack of other rewarding activities(18), as well as because of a relative increase of psychosocial stress, substance use being used as self-medication on the short term. On the other hand, however, there is evidence that substance use may contribute to greater risk of depression on the long term. Regarding alcohol use disorder and MDD, the presence of either disorders doubles the risk of developing the other(19). Beyond alcohol use disorder, alcohol consumption has also been linked to depression(20). Tobacco use may also cause depressive symptoms. In a meta-analysis including several prospective studies, smokers at baseline had 60% greater odds of incident depression at follow-up than subjects having never smoked(21). Regarding cannabis use, most studies tend to focus on its association with psychotic disorders among adolescents and young adults although some prospective studies have also found an association with depression(22).

Given that SES factors, including education and income, may influence substance use, which in turn may increase the risk of depression, substance use appears as a plausible, yet understudied mediator of the association between SES and depression. Furthermore, substance use may also moderate this association. First, low income and/or education may increase the probability of relying on substance use as a coping strategy, thus precipitating depression, chiefly due to a relative lack of other coping strategies, as compared to individuals of higher status(9). Second, substance use may impede emotion regulation abilities, which are more likely to be challenged in individuals of low SES, because of more frequent stressful life events. Third, low SES may be associated with both cognitive and behavioral vulnerabilities for depression that can render individuals more sensitive to the depressive effects of substances(23).

In order to examine the role of prevalent substances (i.e., alcohol, tobacco, cannabis) in the association between education or income and depression, we have used prospective data from a large, population-based cohort, the Constances cohort, and have applied mediation and moderated mediation models in which we hypothesize that SES differences in the prevalence of depressive states may be explained by both differences in the prevalence of alcohol, tobacco, and cannabis according to SES (i.e., mediating effects), and differential effects of substance use on depressive state according to SES (i.e., moderating effects). Because gender may influence both the likelihood of engaging in substance use and developing depressive states(24), all analyses are stratified by gender.

3. Material and methods

1. Sample selection

Constances is a large, population-based, prospective cohort whose recruitment began in 2012 and ended in 2019 with a total size of more than 200,000 subjects, including volunteers aged 18-69 at baseline, and living in 21 selected departments (administrative divisions) throughout metropolitan France, in both rural and urban settings(25). Participants were selected among individuals covered by the general insurance scheme or partner health insurance funds (in all, 85% of the French population) using a random sampling scheme stratified on place of residence, age, gender, and occupational status. Eligible individuals were invited by mail to participate in the study. Volunteers completed a self-administered questionnaire on lifestyle, health status, medical history, and socio-professional status, and attended a Health Screening Center for a comprehensive evaluation including a physical examination and laboratory tests. The Constances cohort study has received the authorization of the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL) and the institutional

review board of the National Institute for Medical Research (Inserm) (Authorization number 910486). All subjects included in this study gave an informed consent.

An annual self-administered follow-up questionnaire is completed by the participants at home, using either a paper or Internet questionnaire. Depressive symptoms were assessed at both inclusion and in the 2015 annual questionnaire.

Inclusion criteria were having had a follow-up in 2015 and a baseline data collection in the years of 2012-2014. The initial sample thus consisted of 51,335 participants with data at baseline collected in the years 2012-2014. In total, 50,608 participants were contacted for follow-up in 2015 (out of which only 37,192 responded and had their data entered – a 73.49% response rate). The present analyses were conducted on 37,192 adult participants (**supplementary Figure 1**).

2. Variables

Age and gender were obtained in the baseline questionnaire.

Income

Income was measured by the following question: “What is the total amount of the net monthly income of your household? (i.e., the sum of all the incomes of people living in your household or your income if you live alone, whatever the source of the income)?”. Participants had to select among the following options: 1) less than 450 euros; 2) 450 to less than 1,000 euros; 3) 1,000 to less than 1,500 euros; 4) 1,500 to less than 2,100 euros; 5) 2,100 to less than 2,800 euros; 6) 2,800 to 4,200 euros 7) more than or equal to 4,200 euros; 8) don’t know how to answer and 9) does not wish to answer.

Since categories 8 and 9 (representing 4.9% of the sample) would not have conveyed much information, they were thus considered as missing and multiple imputation analyses were subsequently run to handle missing data.

Income was thus computed as a seven category variable.

Education

Education was measured using the following question: “What is the highest diploma that you have obtained?”. Participants had to select among the following options: 1) no diploma; 2) general study certificate (equivalent to 12 years of school education); 3) certificate of professional aptitude; 4) high school diploma or equivalent; 5) undergraduate degree (2-3 years of study); 6) graduate degree (4 years of study); 7) graduate degree (≥ 5 years of study) 8) other. Since category 8 (representing 0.19% of the sample) would not have conveyed much information, it was thus considered as missing and multiple imputation analyses were subsequently run to handle missing data. Again, education was computed as a seven category variable.

Alcohol consumption

Chronic alcohol consumption was computed based on the following question: “How often do you usually drink alcoholic beverages?” Participants had to choose one of the following four responses: 1) Never; 2) Once a month or less; 3) Two or three times per month and 4) Once a week or more. For participants who declared a chronic consumption for “once a week or more”, weekly alcohol consumption was computed in drinks per week based on a reporting of all the alcoholic beverages consumed the previous week.

The average number of drinks per day was multiplied by seven in order to get the total number of drinks per week. Non-regular consumption (included abstinent who reported never drinking alcohol) was considered as having less than 1 drink per week. Regular consumers were categorized according to the WHO alcohol risk categories (World Health Organization, 2000) for men (women): 1) low: ≤ 28 (14); 2) medium: $29-42$ (29); 3) high: $43-70$ (43) and 4) very high: ≥ 71 (43). The last two categories were merged to ensure sufficient sample size. The final variable

consisted of four classes: 1) very low risk (abstinent) : <1 (1) drinks/week in men (women); 2) low risk: 1-27 (1-13) drinks/week in men (women); 3) moderate risk: 28-42 (14-28) drinks/week in men (women); 4) high and very high risk: >42 (28) drinks/week in men (women). Missing data on alcohol consumption represented 11% of the sample and were handled using multiple imputation analyses.

Cannabis use

The questionnaire regarding cannabis consumption involved three questions: 1) “Have you ever consumed cannabis”; 2) “Have you consumed cannabis in the past 12 months?” 3) “Have you consumed cannabis in the past thirty days?” Participants had to choose between: yes, no, and does not know. Individuals who have answered “does not know” have been considered as missing (representing 7% of the sample) and values were assigned based on multiple imputations. Those that answered “yes” were further asked how many times they consumed in the past 12 months and 30 days.

From the previous information, a categorical variable expressing the frequency of lifetime cannabis consumption was computed as follows: 1) never used; 2) consumption in the past 12 months, but not in the past 30 days; 3) less than once a week; and 4) one time per week or more.

We conducted imputations conducted for missing cannabis use data.

Tobacco use

Tobacco use status (i.e., non-smoker, former smoker, or current smoker) was self-reported. Participants had to pick from the following: “Smoking status at inclusion: non-smoker, former smoker and current smoker. Among current smokers, the average number of average number of rolled cigarettes, manufactured cigarettes, cigars and cigarillos consumed per day was determined (regardless of the product, e.g., common cigarette, cigar, and pipe) as: 1) less than one per day; or 2) one time per day or more. A further question ““How many times do you

smoke on average per day?” determined the average number of rolled cigarettes, manufactured cigarettes, cigars and cigarillos consumed per day if the participant answered one time per day or more on the former question. From these variables, we computed a categorical variable with five modalities: 1) non-smokers; 2) former smokers; 3) current light smokers (1 to 9 cigarettes per day); 4) current moderate smokers (10 to 19 cigarettes per day); and 5) current heavy smokers (>19 cigarettes per day). We have conducted imputations for missing data on cigarette smoking (representing 5.5% of the sample).

Depressive state at baseline and at follow-up

We measure depressive symptoms using the self-administered Center of Epidemiologic Studies Depression scale (CES-D). This scale evaluates the frequency of depressive symptoms during the previous week (e.g., “I felt depressed”, “I felt everything I did was an effort”, “my sleep was restless”). Responses range from 0 (hardly ever) to 3 (most of the time), resulting in a global score ranging from 0 to 60. Internal consistency of this scale is generally high ($\alpha=0.90$ in the Constances cohort). Depressive state was defined by a CES-D score ≥ 19 , according to the validated cutoff of the French version (sensitivity/specificity for the diagnosis of major depression: 0.85/0.86)(26). We have conducted imputations for missing data (representing 5.6% of the sample at baseline and 3.9% at follow-up).

Depressive symptoms were available at baseline and upon follow-up at one, two or three years depending of the year of recruitment of the subjects in the cohort.

Missing patterns were computed before running multiple imputations analyses and are presented as complementary analyses. The missing pattern was not monotone (Supplementary table 1), and since most variables were categorical, we selected the Fully Conditional Specification (FCS) method as being appropriate for data with arbitrary missing patterns(27). We imputed the

dependent variable (depressive symptoms) and the predictors (alcohol, cannabis, tobacco, income, and education) as part of the logistic regression model and we requested three imputations. For each variable, the rate of missing data, including the responses that we did not categorize (e.g., “I do not want to answer”), ranges from 1.32% to 11.1%, with 85% of participants having no or no more than one missing value (Supplementary table 1). All descriptive statistics, estimates for the logistic regression and SEM models are modeled effects of the three imputations.

Means and frequencies of all variables before imputations are presented as part of the supplementary analyses (supplementary table 2).

In summary, Table 1 shows the characteristics of the population using the means of the 3 imputations as included in the analyses and Supplementary table 2 shows the characteristics of the population without running imputations. Supplementary Table 3a presents descriptive statistics using binary variables after having determined the threshold based on their association with depressive symptoms, stratified for sex and controlling for age.

3. Statistical analyses

We have analyzed associations between baseline variables and depressive states at follow-up (of one, two or three years) using logistic regressions stratified by gender and adjusted for age and presented as odds-ratio (OR) and 95% confidence interval (CI). Next, we used path analysis with mediation in order to examine the extent to which the association between SES (using successively income and education) and depressive states at follow-up is explained by substance use (alcohol, tobacco and cannabis). The mediation model allows for the possibility of compensatory effects, i.e., that some indirect effects through each substance use can be either positive or negative.

The mediation model can fully explain the greater risk of depressive states at follow-up in individuals with low socio-economic status (SES) if the total indirect effect (i.e., the sum of all the specific indirect effects of SES on depressive states through all types of substances) is positive and there is no additional (i.e., direct) effect of SES on risk of depressive states. By contrast, the presence of a significant direct effect of SES on risk of depressive states beyond the indirect effects of SES on depressive states through all types of substances will suggest the existence of differential effects of substance use on risk of depressive states according to SES, i.e., a moderating effect of SES on the effect of substance use on depressive states according to substance use.

To test the presence of this moderating effect while simultaneously taking into account SES differences in the prevalence of substance use, we use a structural equation model with moderated mediation(28-30).This model incorporates a moderating effect of SES (using successively income and education) on the relationship between substance use (alcohol, tobacco and cannabis) and depressive states at follow-up, modeled as an interaction between SES and substance use. The mediation-moderation model helps take into account any residual mediation effect.

Because we have sought to simultaneously examine all path coefficients, no paths in any of the models were fixed to zero. Therefore, goodness of fit measures are not relevant in evaluating these models since they do not inform on the “correctness” of the models, but rather provide only a summary of how well the observed correlations match the model when several paths are fixed at zero(31).

In all models, we use binary variables for which the choice of the threshold is based on preliminary analyses regarding their associations with depressive states at follow-up, while

adjusting for age and depressive states at baseline and stratifying for gender (Figures 1-4 and Supplementary Tables 3a and 3b). This method was chosen in order to maximize the estimates with depressive states and the possibility of observing significant mediation and moderation effects.

For each variable, the selected threshold corresponds to the category for which the association is significant in men as well as in women; the same category, which may correspond to different levels of consumption for alcohol, is then used in both men and women. These thresholds re: >42 (28) drinks per week for men (women) for alcohol, ≥ 10 cigarettes per day for both men and women for smoking, and >4 times/30 days for both men and women for cannabis use. Low education is defined as having a high school diploma, and lower and low income are defined as boasting a household income less than 2,800 euros for both men and women.

We acknowledge that the cut-off used for the definition of low income does not meet the definition of 'low income' in France and is not a standard measure. For the sake of simplicity, we use this term throughout the text and the figures in order to refer to an income ranging between 2100 and 2800 euros.

We conducted all our analysis using Mplus Version 7.1(32). This software provides estimates and tests of significance for direct effects, as well as specific and total indirect effects. The default estimator for the analysis is the weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical and dichotomous variables and appropriate for large sample sizes(32, 33). Standardized estimates indicate how many standard deviations higher (or lower) from the mean of the latent variable underlying the binary outcome are expected to be for each increase in an additional unit of the binary predictor, while adjusting for age and depressive

states at baseline. Other analyses were carried out with the Statistical Analysis System (SAS, version 9.4, Cary NC). We have evaluated statistical significance with α set *a priori* at 0.05.

4. *Supplementary analyses*

First, to determine whether focusing on alcohol consumption rather than alcohol use disorder might have led to underestimate the observed effects, we computed the mediation models using the total score of the Alcohol Use Disorders Identification Test (AUDIT) in order to assess the risk of alcohol use disorder at baseline. To this end, the AUDIT total score was categorized into 1) Mild (0–7), 2) Dangerous (8–15), 3) Problematic (16–19), and 4) Dependence (20–40). Then, the association of the AUDIT score with depressive symptoms was examined in order to further categorize it into a binary variable. The AUDIT score was aggregated as a binary variable as follows: mild risk (0–7) versus at-risk (8–40) alcohol use. This binary variable was entered in the mediation models.

To check whether focusing on very high alcohol consumption (i.e. ≥ 71 (43) drinks per week for men/women) could be more sensitive than high alcohol consumption in detecting meaningful differences compared with lower consumption, we have repeated the mediation models using this higher cut-off. Moreover, to check whether focusing on a household income less than 2100 euros could be more sensitive than a household income less than 2800 euros, we have repeated the mediation models using this lower cut-off to define low income.

Second, we performed a series of sensitivity analyses to test the robustness of our results. We reproduced the main analyses while excluding participants with at least one missing data. As some young adults, not coming from a low SES background but still enrolled in an education program (with no degree completion yet), may bias the association between low education status and depressive symptoms, we have chosen to also conduct sensitivity analyses by removing participants aged 25 years or less. We have also conducted mediation analyses by year of

inclusion in the cohort to account for differences in duration of follow-up. Finally, we have conducted sensitivity analyses while removing alcohol abstinent participants.

5. Results

1. *Participants' characteristics*

Table 1 presents the descriptive characteristics of the population stratified for gender. The prevalence of individuals holding a high school diploma equivalent or less is 43.9% in men and 41.4% in women. Income of less than 2,800 euros is prevalent in 33.1% and 41.0% of men and women respectively. A high-risk alcohol use concerns 2.4% and 1.2% of men and women, respectively. Tobacco use of more than or equal to ten cigarettes per day is prevalent in 8.7% and 6.8% of men and women, respectively. Cannabis use of at least four times in thirty days concerns 4.4% and 2.2% of men and women, respectively.

2. *Age-adjusted association with depressive states*

Table 2 presents the age-adjusted associations of baseline variables with depressive states at years one, two, and three. There is an obvious negative gradient between SES indicators and the risk of depressive states (Table 2). When considering the selected thresholds (supplementary Table 3b), the OR of depressive states with lower income are 2.19 (95% CI 1.98-2.42), and 1.88 (95% CI 1.74-2.03) for men and women, respectively. Likewise, men and women in the lower category of education exhibit higher odds of depressive states (OR 1.47, 95% CI 1.34-1.61, and OR 1.45, 95% CI 1.35-1.55, respectively).

Similarly, substance use show obvious gradients (Table 2). When considering the selected thresholds, smoking 10 cigarettes or more per day appears to be associated with depressive states: OR 2.17 95% CI 1.88-2.49, and OR 1.88 95% CI 1.65-2.14 in men and women, respectively.

Likewise, drinking more than 42 (28) drinks/week for men (women) is associated with depressive states in men (OR 2.55 95% CI 2.03-3.21), and women (OR 1.39 95% CI 1.03-1.87).

The association of cannabis use with depressive states is significant in both men and women

when smoking cannabis at least once in the last thirty days (OR 1.52 95% 1.24-1.86 and OR 1.37 95% CI 1.11-1.69), for men and women respectively.

3. Mediation analyses

Estimates from the path analysis are shown in Figures 1a, 1b, 2a, 2b for education and income in both genders, respectively. All figures display specified direct effects unless otherwise specified.

Education

In men, the associations between low education and substance use are significant for alcohol and tobacco use, but not for cannabis use (Figure 1a). The associations between substance use and depressive states are significant for tobacco use. In women, the significant associations concern tobacco use only, with low education on one hand, and depressive states on the other hand (Figure 1b).

In men and women, the standardized total effect of low education on depressive states is 0.12 ± 0.03 and 0.09 ± 0.02 , respectively ($p < 0.05$). The total indirect effect through substance use is negligible (0.01 ± 0.00 and 0.00 ± 0.00 in men and women, respectively). Accordingly, the ratio of total indirect effect (mediated through substance use variables) on total effect (i.e., the direct effect of low income on depressive states, plus the total indirect effect mediated through substance use variables) amounts to $0.007/0.131=5.34\%$, and $0.002/0.096=2.42\%$ for men and women, respectively. In other words, for men, less than 6% of the association between low education and depressive states is explained by alcohol, tobacco, and cannabis use. For women, the role of substance use in the association between low education and depressive states is even weaker, at less than 3%.

Income

For men (Figure 2a) and women (Figure 2b), the association between income and substance use is significant for alcohol and tobacco, but not cannabis. For men, tobacco use is associated with

depressive states. Additionally, for men and women, the standardized total effect of low income on depressive states is 0.17 ± 0.03 , and 0.27 ± 0.02 , respectively ($p < 0.05$). The standardized indirect effect is 0.004 ± 0.0003 in men, and -0.004 ± 0.002 in women, and did not reach statistical significance. In other words, mediation models indicate that substance use does not explain the association between low income and depressive states.

4. Moderated mediation analyses

Estimates from the mediation and moderation models are shown in Figures 3a, 3b, 4a, 4b for education and income in both genders, respectively. All figures display specified direct effects unless otherwise specified

Education

Direct effects between low education and depressive states and the total indirect effect have appeared non-significant in the presence of modeled interactions between low education and substance use. The total moderating effect is significant, at 0.28 ± 0.08 and 0.18 ± 0.09 , in men (Figure 3a) and women (Figure 3b) respectively, indicating that the effect of substance use on depressive states is significantly greater in participants with low education. Because tobacco is the only substance with a significant mediation effect and for which the moderation effect of SES is the strongest in both genders, our results suggest that tobacco use may play a substantial role in the association between low education and depressive states in both genders.

Income

Direct effects between low income and depressive states and the total indirect effect seem non-significant in the presence of modeled interactions between low income and substance use. In contrast, the moderation effect is largely significant in both men and women (Figures 4a and 4b). The total moderating effect is significant, at 0.35 ± 0.08 and 0.25 ± 0.08 for men and women respectively, indicating that the effect of substance use on depressive states is significantly

greater in participants with low income. Similarly, because tobacco is the only substance with a significant mediation effect and for which the moderation effect of SES is the strongest in both genders, our results suggest that tobacco use may play a substantial role in the association between low income and depressive states in both genders.

5. Supplementary analyses

First, the mediation analyses results using the AUDIT score (binary variable) instead of alcohol consumption are presented in Supplementary figures 2-5 and were similar to the ones obtained using alcohol consumption.

Second, we have performed a series of sensitivity analyses to examine the robustness of our results. We first compared the results obtained with and without missing data imputation. The descriptive characteristics of the population without imputations are displayed in Supplementary Table 2. Alcohol consumption, tobacco and cannabis use frequencies and results of mediation and moderated mediation models are similar when excluding participants with missing data (Supplementary Tables 3a, 4 and 5).

Moreover, we ran the analyses of mediation and moderated mediation models without inclusion of depressive state at baseline and have surcharged similar results that are presented in Supplementary Tables 6 and 7.

Given that education levels for individuals younger than 25 may not reflect future achievements, we have reproduced those analyses and have reached similar findings (supplementary Table 8). Since alcohol abstinence may signal underlying mental or physical conditions that may partially blur the analysis, we have redone those analyses while excluding those participants, and have identified results leading to similar interpretation (supplementary Table 9).

The mediation analyses results using very high alcohol consumption (binary variable) instead of high alcohol consumption are presented in Supplementary figures 6-9 and were similar to the ones obtained using a lower threshold of alcohol consumption. Additionally, The mediation analyses results using a lower cut-off for income (binary variable) instead of a higher cut-off, are presented in Supplementary figures 10-11 and were similar to the ones used with the higher cut-off.

Finally, since we had three years of inclusion in the cohort (2012, 2013, and 2014) and hence a different duration of follow-up, we have reproduced these analyses stratified by year of inclusion and have observed similar findings (supplementary Tables 10a and 10b).

6. Discussion

1. Main findings

In a large population-based cohort study, we have examined the extent to which the association between low SES and depressive states can be explained by higher prevalence of consumption of alcohol, tobacco or cannabis, or differential effects of substances use on depressive states (measured according to SES). Contrary to our expectations, our results show a significant, but clinically negligible (i.e., <6% of the total effect for men, and <3% in women) mediation effect of substance use in the association between low education and depressive states. Regarding the association between low income and depressive states, mediation effect was not even significant. These findings suggest that SES differences in substance use are unlikely to explain higher rates of depressive states in individuals with low SES. However, moderated mediation analyses reveal that the effect of substance use on depressive states, and particularly tobacco use, which is the only substance with a significant mediation effect and for which the moderation effect of SES is the strongest in both genders, is significantly greater in participants with low SES. This finding

suggests that the strong effect of tobacco use on depressive states in individuals with low SES may substantially explain the association between low SES and depressive states in both genders. Sensitivity analyses have yielded similar results, thus reinforcing our findings.

2. Strengths and limitations

The strengths of our study include the large sample and the design of the Constances cohort that have allowed us to study different associations among SES status, depressive states and substance use. To our knowledge, this is the first study to explore and quantify the mediation and moderation effects of substance use in the relationship between SES and depressive states in a large population-based sample of randomly recruited men and women. Additionally, we have explored mediation and moderation effects together and have been able to refine our understanding of the interplay between SES and substance use regarding depressive states and substances were allowed to correlate.

Limitations include the partially cross-sectional nature of the data which restricts the possibility of drawing causality with regards to associations between SES and substance use. For instance, our results clearly suggest that SES and substance use interact in predicting subsequent depressive states, but their relationships being likely bidirectional, it remains difficult to disentangle their respective effects on depressive states. However, we have measured the outcome of interest (i.e., depressive states) at both baseline and follow-up, so we have had a prospective understanding of the direction of its associations with predictors in the model.

Second, we have not assessed major depression in the present study. However, although our main proxy for depression is based on a well-validated measure of depressive states (26), our results may not apply on individuals with major depression, but rather on the larger population of those experiencing depressive states. Third, we have not adjusted for income for household size in our study. Since income was measured through pre-defined response categories, it was not

possible to precisely calculate net income per individual living in the household. Therefore, the number of family members was not considered in our analyses, reducing the sensitivity of our measure. Fourth, our models have not taken into consideration further confounding variables such as chronic conditions or marital status, which are simultaneously related to SES and substances consumption; this is because our main purpose has been to quantify the mediating and moderating role of substance use between SES and depression, and not to study their association per se. Unemployment has been linked to depression and substance use but it may not indicate the presence of low education or low income and applies only to individuals in the workforce. Therefore, it was not considered in the present analyses. Besides, we have chosen the least number of factors possible in order to keep our models simple and easy to interpret.

Moreover, this paper focuses on substance consumption in quantitative terms rather than qualitative terms. Information related to substance use such as heavy drinking, loss of control and craving which we have not taken into consideration in the present study, may be more robust factors associated with depression, which limits the weight of alcohol and cannabis in this study. However, analyses based on the AUDIT score assessing the risk of alcohol use disorder at baseline in the mediation models did not show significant results in their association with education/income or depressive states. Cannabis consumption was only provided quantitatively so further qualitative analyses were not possible.

Analyses conducted when using very high alcohol consumption in the mediation models did not show significant results in their association with education/income or depressive states. Moreover, analyses conducted when using a lower cut-off for income in the mediation models yielded similar results.

Regarding tobacco consumption, even though they are associated with depressive states, the number of pack-years were not included in our analyses for assessment of tobacco consumption because they are associated to past consumption and thus may more loosely relate to current depressive states than current consumption.

Additionally, even though the Constances cohort was designed as a randomly selected representative sample of French adults, the current sample may not be representative of the general population. This might partly explain the relatively low prevalence of smoking, as this may be linked to the presence of health-concerned participants.

Lastly, the study has sought to balance parsimony with explanatory power. Future work may incorporate additional mediating and moderating variables, or integrate different levels of analysis (e.g., genetics or neuroimaging).

3. Explanatory hypotheses

Contrary to our expectations, substance use does not appear to substantially mediate the association between education or income and depressive states. It is noteworthy that this absence of substantial mediation is not explained by a lack of associations between SES or substance use and depressive states, which are mostly significant in our study and in line with prior findings(3, 10). Indeed, before concluding that substance use has no role in this association, the possibility of moderation effects also needs to be systematically investigated. When allowing substance use to moderate the effects of income or education, there appears to be a significant interaction between education or income and tobacco use, thereby indicating that tobacco use is more strongly associated with depressive states in individuals with low income or education. Our data are consistent with the hypothesis that individuals with low income or education may experience greater vulnerability to the effects of tobacco use on depressive states. Several factors may contribute to this greater vulnerability. First, this interaction may be due to tobacco use *per se*

and be explained by biological and/or behavioral factors. Second, tobacco use could be a proxy for a higher-level, unmeasured factor that can be the actual moderator of the SES effects.

Tobacco use may reduce the ability to cope with stressful life events(34), that are more frequently encountered by individuals of low SES(35, 36). There is evidence that nicotine *per se* may be associated with increased vulnerability for depression with a dose-response relationship independently of other tobacco compounds(37). In addition, low SES may be associated with both cognitive and behavioral vulnerability for depression that can render individuals more sensitive to the depressive effects of nicotine deficits(23). Since nicotine is highly associated with neurocognitive impairment, and since individuals coming from low SES background are more prone to stress, mental and anxiety disorders, this will make them more vulnerable (compared to those coming from a higher social class) to the effect of substance use (i.e., tobacco use in our study) with regards to the development of depressive states.

Moreover, besides the intrinsic effects of tobacco use, the moderation of the association between substance use and depressive states can be explained by an unmeasured confounding factor. For instance, temperamental vulnerability for tobacco use may also predict depression. Simply put, nicotine consumption can be associated with (without being the sole cause of) a reduced ability to cope with stressful life events more frequently encountered by individuals of low SES. According to some researchers, tobacco use is a manifestation of the maladaptive response to emotion states(38). SES status has also been shown to affect the relation of emotional disorder to tobacco use, as well as other behaviors such as obesity(39). This hypothesis of a shared vulnerability between substance use and depression that can be more frequently revealed in individuals facing social adversity is also consistent with the moderation by alcohol use that we have observed for low income male participants.

However, compared to tobacco use, our results have not shown substantial mediation and moderation effects regarding alcohol and cannabis consumption. The latter has a well-established association with mood and depressive disorders(40) but, from what we have found from the mediation moderation analyses, the association between these substances (cannabis and alcohol) does not seem to be different across socioeconomic status.

Concluding remark: Our findings show that the strong association of low SES with subsequent depressive states is not substantially explained by increased substance use but rather by the strong effect of tobacco use on depressive states in individuals with low SES. Regarding public health and clinical practice implications, these results suggest that substance withdrawal, particularly nicotine, will be especially advantageous for individuals of low SES in reducing depressive states but, at the same time, may be unlikely to reduce substantially the risk of depression in those of high SES, probably because of the presence of other risk factors associated with low SES. Tobacco use might also be perceived by some individuals as a way to cope with stressful life events for a lack of more elaborated strategies, especially in individuals of lower SES, thus accounting for both mediation and moderation effects. Smoking cessation could also be associated with increased stress level due to withdrawal symptoms thus pointing the potential role of nicotine replacement in preventing depressive symptoms in this vulnerable population. The findings also suggest the importance of prevention strategies (more specifically for tobacco use) in low SES groups. Future studies ought to investigate the exact mechanisms underlying the association between tobacco use and depressive states among individuals with low SES.

Acknowledgements

The authors thank the INSERM-Versailles Saint Quentin en Yvelines University "Population-based Epidemiologic Cohorts Unit" (Cohortes épidémiologiques en population) that has designed and manages the Constances Cohort Study. They also thank the National Health Insurance Fund ("Caisse nationale d'assurance maladie", CNAM) and its Health Screening Centres ("Centres d'examens de santé"), which have collected a large part of the data, as well as the National Old-Age Insurance Fund (Caisse nationale d'assurance vieillesse) for its contribution to the constitution of the cohort, ClinSearch, Asqualab and Eurocell, which are conducting the data quality control.

Funding: The Constances Cohort benefits from a grant from ANR (ANR-11-INBS0002). Constances is also partly funded by MSD, AstraZeneca and Lundbeck. This research was supported by a grant (IReSP-17-PREV-10) from the funding partners of the "Institut de Recherche en Santé Publique" (IReSP) within the framework of the 2017 General Call for Proposal - Prevention topic.

Declaration of interest

Dr Hoertel has received personal fees and non-financial support from Lundbeck, outside the submitted work. Frederic Limosin has received honoraria for consultant/board participation for Janssen-Cilag, outside the submitted work.

Cédric Lemogne has received speaker and consulting fees from Boehringer Ingelheim, Janssen-Cilag, Lundbeck and Otsuka, outside the submitted work.

The other authors have nothing to declare.

Contributors:

JM and CL take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. JM and CL designed the study; MG and MZ

acquired the data; JM, NH and CL performed statistical analysis. All authors contributed to the interpretation of data. JM and CL drafted the article; NH, GA, EW, FL, MG and MZ revised it critically for important intellectual content.

All authors have read and approved the final manuscript.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1: Descriptive characteristics after imputations (mean of the three imputations)

Variables	Men (N=16861)	Women (N=20331)
Income		
<450 euros	100 (0.59)	127 (0.62)
450 to less than 1000 euros	395 (2.34)	620 (3.05)
1000 to less than 1500 euros	874 (5.18)	1447 (7.12)
1500 to less than 2100 euros	1603 (9.51)	2624 (12.90)
2100 to less than 2800 euros	2610 (15.47)	3524 (17.33)
2800 to less than 4200 euros	5479 (32.49)	6439 (31.67)
≥4200 euros	5797 (34.38)	5547 (27.28)
Education		
No diploma	442 (2.62)	423 (2.08)
General study certificate (equivalent to 12 years of school education)	1102 (6.53)	1574 (7.74)
Certificate of professional aptitude	3308 (19.62)	2754 (13.54)
High school diploma or equivalent	2554 (15.14)	3677 (18.08)
Undergraduate degree (2-3 years of study)	3565 (21.14)	5828 (28.66)
Graduate degree (4 years of study)	1410 (8.36)	2098 (10.31)
Graduate degree (≥5 years of study)	4479 (26.56)	3975 (19.55)
Age	51 ± 0.09	49 ± 0.09
Alcohol		
Very low: <1(1) drinks/week in men(women)	2602 (15.43)	6298 (30.97)
Low: 1-27(1-13) drinks/week in men(women)	12675 (75.17)	11925 (58.65)
Medium: 28-42(14-28) drinks/week in men(women)	1178 (6.98)	1857 (9.13)
High: >42(28) drinks/week in men(women)	405 (2.40)	250 (1.22)
Smoking		

Non-smoker	6948 (41.20)	10841 (53.32)
Ex-smoker	7297 (43.27)	6490 (31.92)
Current smoker		
• Low: 1-9 cigarettes/day	1146 (6.80)	1605 (7.85)
• Medium: 10-19 cigarettes/day	989 (5.86)	1099 (5.4)
• High: ≥ 19 cigarettes/day	479 (2.84)	295 (1.45)
Cannabis		
No consumption	15554 (92.25)	19396 (95.4)
Consumption but not in the past 30 days	560 (3.32)	469 (2.30)
Consumption in the past 30 days but $< 4/30$ days	421 (2.49)	293 (1.44)
Consumption in the past 30 days and $\geq 4/30$ days	325 (1.93)	172 (0.84)
Depressive symptoms		
CESD baseline (N used=35087)	9.1 \pm 0.06	11. \pm 0.06
Depressive symptoms baseline (CESD ≥ 19)	1727 (10.24)	3800 (18.69)
CESD follow-up (N used=35741)	10 \pm 0.06	13 \pm 0.06
Depressive symptoms follow-up (CESD ≥ 19)	2231 (13.23)	4676 (23)
Variables	Men (N=16,861)	Women (N=20,331)
Income		
<450 euros	100.33 (0.59)	127.66 (0.62)
450 to less than 1,000 euros	395.66 (2.34)	620.33 (3.05)
1,000 to less than 1,500 euros	874 (5.18)	1,447.66 (7.12)
1,500 to less than 2,100 euros	1,603.66 (9.51)	2,624.66 (12.90)
2,100 to less than 2,800 euros	2,610 (15.47)	3,524 (17.33)
2,800 to less than 4,200 euros	5,479.66 (32.49)	6,439.66 (31.67)
$\geq 4,200$ euros	5,797.66 (34.38)	5,547.0 (27.28)
Education		
No diploma	442 (2.62)	423.66 (2.08)
General study certificate (equivalent to 12 years of school education)	1,102 (6.53)	1,574 (7.74)

Certificate of professional aptitude	3,308.33 (19.62)	2,754.33 (13.54)
High school diploma or equivalent	2,554 (15.14)	3,677 (18.08)
Undergraduate degree (2-3 years of study)	3,565 (21.14)	5,828.66 (28.66)
Graduate degree (4 years of study)	1,410.66 (8.36)	2,098 (10.31)
Graduate degree (≥ 5 years of study)	4,479 (26.56)	3,975.11 (19.55)
Age	51.06 \pm 0.09	49.26 \pm 0.09
Alcohol		
Very low: <1(1) drinks/week in men(women)	2,602.66 (15.43)	6,298.33 (30.97)
Low: 1-27(1-13) drinks/week in men(women)	12,675 (75.17)	11,925 (58.65)
Medium: 28-42(14-28) drinks/week in men(women)	1,178 (6.98)	18,57.33 (9.13)
High: >42(28) drinks/week in men(women)	405.33 (2.40)	250 (1.22)
Smoking		
Non-smoker	6,948 (41.20)	10,841 (53.32)
Ex-smoker	7,297.33 (43.27)	6,490 (31.92)
Current smoker		
• Low: 1-9 cigarettes/day	1,146.66 (6.80)	1,605.33 (7.85)
• Medium: 10-19 cigarettes/day	989.33 (5.86)	1,099.33 (5.4)
• High: ≥ 19 cigarettes/day	479.66 (2.84)	295 (1.45)
Cannabis		
No consumption	15,554 (92.25)	19,396 (95.4)
Consumption but not in the past 30 days	560 (3.32)	469.33 (2.30)
Consumption in the past 30 days but <4/30 days	421 (2.49)	293 (1.44)
Consumption in the past 30 days and $\geq 4/30$ days	325.66 (1.93)	172.66 (0.84)
Depressive symptoms		
CESD baseline (N used=35,087)	9.1 \pm 0.06	11.76 \pm 0.06
Depressive symptoms baseline (CESD ≥ 19)	1,727 (10.24)	3,800.33 (18.69)
CESD follow-up (N used=35,741)	10.28 \pm 0.06	13.12 \pm 0.06

Depressive symptoms follow-up (CESD \geq 19)	2,231 (13.23)	4,676.33 (23)
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Results are presented as mean estimate (percent) and mean \pm SEM as appropriate.

Table 2: Association of depressive state with SES and substance use variables in men and women controlling for age

	OR 95% CI	
	Men	Women
Education		
No diploma	3.09 (2.35-4.06)	2.68 (2.13-3.37)
General study certificate (equivalent to 12 years of school education)	1.96 (1.61-2.38)	1.88 (1.62-2.17)
Certificate of professional aptitude	1.63 (1.42-1.88)	1.66 (1.47-1.87)
High school diploma or equivalent	1.34 (1.15-1.55)	1.40 (1.25-1.56)
Undergraduate degree (2-3 years of study)	1.15 (1.00-1.32)	1.18 (1.06-1.31)
Graduate degree (4 years of study)	1.37 (1.12-1.69)	1.10 (0.96-1.27)
Graduate degree (≥ 5 years of study)	1	1
Income		
<450 euros	4.49 (2.84-7.09)	3.06 (2.06-4.53)
450 to less than 1,000 euros	6.19 (4.85-7.90)	3.89(3.15-4.80)
1,000 to less than 1,500 euros	3.60 (2.93-4.41)	2.95 (2.56-3.40)
1,500 to less than 2,100 euros	2.35 (2.00-2.76)	2.16 (1.91-2.46)
2,100 to less than 2,800 euros	1.70 (1.47-1.97)	1.76 (1.58-1.96)
2,800 to less than 4,200 euros	1.23 (1.07-1.42)	1.34 (1.21-1.47)
$\geq 4,200$ euros	1	1
Cannabis		
Not at all	1	1
In the past 12 months but not in the past 30 days	1.39 (1.10-1.75)	1.18 (0.97-1.93)
<4times/30 days	1.31 (1.00-1.72)	1.40 (1.06-1.84)
≥ 4 times/30days	1.92 (1.46-2.52)	1.37 (0.97-1.93)
Alcohol		
Very low: <1(1) drinks/week in men(women)	1	1
Low: 1-27(1-13) drinks/week in men(women)	0.82 (0.72-0.93)	0.83 (0.77-0.90)
Medium: 28-42(14-28) drinks/week in men(women)	1.07 (0.88-1.31)	1.10 (0.98-1.24)
High: >42(28) drinks/week in men(women)	2.26 (1.72-2.87)	1.27 (0.93-1.72)
Smoking		
Non-smoker	1	1

Ex-smoker	1.20 (1.08-1.34)	1.06 (0.97-1.17)
Current smoker		
• Low: 1-9 cigarettes/day	1.12 (0.90-1.40)	1.23 (1.09-1.39)
• Medium: 10-19 cigarettes/day	1.95 (1.61-2.38)	1.78 (1.55-2.05)
• High: ≥ 19 cigarettes/day	3.40 (2.70-4.28)	2.77 (2.10-3.66)

Cut-off corresponding to the category for which the association was significant in men as well as in women; the same category was then used in both men and women.

Figure 1a: Simple mediation model of the relationship between education, substance use and depressive states in men (N=37,192)

Figure 1a legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects=0.007 (0.002) $p < 0.05$. Total effects=0.131 (0.027) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Figure 1b: Simple mediation model of the relationship between education, substance use and depressive states in women (N=37,192)

Figure 1b legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects=0.002 (0.001) $p < 0.05$. Total effects=0.096 (0.022) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Figure 2a: Simple mediation model of the relationship between income, substance use and depressive states in men (N=37,192)

Figure 2a legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects=0.004 (0.003) not significant. Total effects=0.175 (0.028) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Figure 2b: Simple mediation model of the relationship between income, substance use and depressive states in women (N=37,192)

Figure 2b legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects=-0.004 (0.002) not significant. Total effects=0.268 (0.021) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Figure 3a: Moderated mediation model of the effects of education and substance use on risk of depressive states in men (N=37,192)

Figure 3a legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects = -0.01 (0.002) not significant. Moderation effect = 0.278 (0.076) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Dotted arrows indicate moderation effects of low education on the relationships between each substance and risk of depressive symptoms; e.g, the effect of smoking ≥ 10 cigarettes per day on risk of depressive symptoms is higher in participants with low education (0.05 + 0.09) than in those with higher education (0.05).”

Figure 3b: Moderated mediation model of the effects of education and substance use on risk of depressive states in women (N=37,192)

Figure 3b legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects = -0.002 (0.001) $p < 0.05$. Moderation effect = 0.182 (0.09) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Dotted arrows indicate moderation effects of low education on the relationships between each substance and risk of depressive symptoms.

Figure 4a: Moderated mediation model of the effects of income and substance use on risk of depressive states in men (N=37,192)

Figure 4a legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects = -0.008 (0.003) not significant. Moderation effect = 0.348 (0.076) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Dotted arrows indicate moderation effects of low education on the relationships between each substance and risk of depressive symptoms.

Figure 4b: Moderated mediation model of the effects of income and substance use on risk of depressive states in women (N=37,192)

Figure 4b legend:

Depressive states defined by a CES-D score ≥ 19 for men and women according to the validated cutoff of the French version

Regression coefficients are standardized. Values in brackets are standard errors. All coefficients in bold are significant (2-sided $p < 0.05$).

Indirect effects = -0.002 (0.002) not significant. Moderation effect = 0.247 (0.08) $p < 0.05$.

Reference groups used for substance binary variables are ≤ 42 drinks per week for alcohol, < 10 cigarettes per day for smoking, and ≤ 4 times/30 days for cannabis use.

Mediators (i.e., alcohol, tobacco, cannabis) were allowed to correlate with each other.

Dotted arrows indicate moderation effects of low education on the relationships between each substance and risk of depressive symptoms.















