Author's response to reviews

Title: Predictors of onset of cannabis and other drug use in male young adults: Results from a longitudinal study

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Author's response to reviews: see over
Dear Editor, dear Reviewers,

Thank you very much for the helpful comments and recommendations we received with regards to our manuscript “Predictors of the late onset of cannabis and other drug use in male young adults”. We have addressed all of your comments (see following pages) and revised our manuscript considering your suggestions.

We look forward to hearing from you.

Yours sincerely,

Severin Haug
Reviewer 1: Maria Neumann

Minor Essential Revisions

Background:
1. What is the reference in the first sentence? 230 mill individuals worldwide?

Author Response:
Thanks. This sentence (page 3, first paragraph) has been rewritten in order to clarify that it refers to 230 million individuals of the world's adult population between the ages of 15 and 64.

Methods:
2. The variable label “psychiatric problem of... [e.g. father]” can be misleading from the actual measure. Can it be renamed into a more precise label, e.g. “Psychiatric problems that demanded treatment”?

Author Response:
Thanks. We amended added that the variable refers to lifetime prevalence of a psychiatric, alcohol or drug problem of the parents that demanded treatment (page 9, 1st paragraph).

3. Measures of substance use: Maybe the selection of cut-off-values could be justified here, especially where they differ from commonly used cut-offs.

Author Response:
For the AUDIT-C and the CUDIT we selected commonly used cut-offs as suggested in


and


In order to have enough statistical power for the regression analyses (n per cell) we only used one cut-off for the FTND dividing persons with very low nicotine dependence from persons with low, moderate or high nicotine dependence. On page 9, second paragraph from the bottom, we added the following sentence: “To have enough statistical power for the regression analyses we only divided smokers with very low low nicotine dependence (FTND score 0-2) from smokers with low, moderate or high nicotine dependence (FTND score 3-10).”
Discussion:

4. Be cautious with causal language: “Siblings are able to influence…”

Author Response:

Thanks. We rewrote this sentence (last paragraph on page 12).

Having siblings was identified as risk factor for substance use initiation, especially when they are older or share common characteristics with the consumer [4].

5. “This is in line with previous studies …, whereas … have been found to be protective factors against marijuana use [34].” I have difficulties to understand the meaning of this sentence.

Author Response:

This sentence was modified as follows on page 12, last paragraph

“This is in line with previous research based on cross-sectional data showing that single dimensions of religiosity, namely, social religiosity and perceived religious support, were correlated with lower cannabis use [45].”

6. As you chose to examine use onset along two different groups of substances, a closing statement on whether and where and maybe why predictors for cannabis use initiation differ from those of other illegal substances, might be desirable.

Author Response:

We addressed this point with referring to studies that demonstrated differences in the onset of cannabis and other illicit drug use in the following sentences in the background on page 3: “Although cannabis use in adolescence can increase the risk for the onset of other drug use ( ) the differentiation between the onset of cannabis and other drug use was rarely made in risk factor analyses. This might be especially important in the case of Switzerland where cannabis is rather widespread compared to other illicit drug use in young males ( ).”

Discretionary Revisions

Language:

7. The terms ‘drugs’, ‘licit/illicit’, ‘legal –’ and ‘illegal substances’ are not used consistently; I suggest the consistent use of the terms ‘legal’ or ‘illegal substance’ to avoid moral dimensions.

Author Response:

Thanks. We consistently used the term legal/illegal drugs instead of licit/illicit drugs. However, when also including legal substances like tobacco or alcohol we used the more general term “substance”.
8. Sometimes marijuana is used instead of cannabis: this should be consistent.

**Author Response:**
*Thanks. We consistently used the term “cannabis”.*

Background:

9. Be careful: there are studies on cannabis onset in young adulthood; e.g.

**Author Response:**
*As suggested, this study has been included.*

10. References for predictors on cannabis use onset come from different kinds of studies, including clinical and cross-sectional samples. It should be considered to integrate more evidence from longitudinal, prospective studies.

**Author Response:**
The following additional longitudinal, prospective studies were included in the Background section.


11. “Late onset of use” as a central concept should be clearly defined. Maybe it could be substantiated, e.g. “young adult onset of use”

**Author Response:**
*“Late onset of use” has been defined as “onset of use at adulthood” in third paragraph of the Background section (page 4).*

12. Aetiological models mainly refer to sequencing of substance use initiation, but not to other variables that are examined, e.g. psychosocial variables. Is this because an interest of the publication is in the comparison between the two
groups of substances? Then this should be pointed out more clearly. Otherwise, one or two other core psychological models could be mentioned here, e.g. vulnerability-stress-model.

**Author Response:**
The major models in this area are the “gateway hypothesis” and “the common liability to addiction model”. Both are described in the second paragraph on page 4. Within the subsequent paragraph on page 4 we mentioned limitations of the previous studies referring to these models and amended that prevention practice might benefit from an explorative approach considering a comprehensive set of variables derived from both models:

13. It would be desirable to justify in brief why only men are included and what difference might be expected if women were considered (This is also a point for discussion).

**Author Response:**
In the limitations section (page 14, second paragraph) we added that one limitations of the study is that only men were included, as only young men have to visit the army recruitment centres.

14. Why was cannabis treated separately from all other illegal substances? The aims of the paper should be carved out more clearly.

**Methods:**

**Author Response:**
In line with the introduced relevance for the distinction between cannabis and other drug use in point 6 we formulated the aims more precise: “… with the onset of cannabis and the onset of other illegal drug use separately in male young adults.” (last paragraph of the Background section)

15. Has the illegal substance group been controlled for cannabis use?

**Author Response:**
Yes, within the multivariate models (see also Table 4), we controlled for cannabis use.

16. Health: explain, why SF12 and MDI? Why was major depression measured, but not externalising disorders, although they have been outlined as risk factors in the Background? The consequences of this measurement selection on findings should be communicated and discussed!

**Author Response:**
The C-SURF study aimed at considering all major risk factors for substance use. However, due to the length of the questionnaire short versions of the instruments were preferred given that they had good psychometric properties. Major components of externalising disorders were also included by the
variables measuring attention deficit syndrome (see health variables) anti-social personality disorder (see health variables) and aggression (see Personality variables).

A full list of instruments and corresponding references can be found on www.c-surf.ch. Instruments were chosen based on recommendation of the World Health Organization, because they have been shown to be valid in different languages, or based on literature research appeared to be the most often used.

17. Personality: Why is peer pressure in this category and not under social context?

**Author Response:**

Thanks. Peer pressure was switched to the category “social context”. Furthermore, we switched “adult attention deficit syndrome” and “anti-social personality disorders” to the category “health”. Based on these changes, we recalculated the multivariate models (Tables 3 and 4) however the results of the final multivariate models remained similar as in the previous version.

18. Analysis: Which substances are included in (5) substance use? E.g. is cannabis included in the “substance use” outcome?

**Author Response:**

Yes, but only within the multivariate models of the onset of drug use other than cannabis (table 4).

Discussion:

19. The formulation of the main finding (2) “the following variables are the most relevant...” might be somewhat irritating, because it can suggest, that e.g. depression was a main predictor in contrast to other mental disorders. However, other disorders were not examined in detail. Is depressiveness a specific risk for the outcome or would any (other) mental disorder (better) relate to use initiation?

**Author Response:**

The formulation of this main finding regarding to the onset of cannabis consumption does not mean that the variables described are compared with other variables in the same area, e.g. depression in comparison with other mental disorders. The main idea is that, of those variables that have been analyzed in our study, the following are the most important in order to predict the onset of cannabis use. Therefore, the sentence has been rewritten as follows: “Of those variables that have been studied, the following are the most relevant to predict the onset of cannabis use: ...” (see Discussion, first paragraph)
20. “This result is in line with the gateway hypothesis and the common liability of addiction theory”? This conclusion is not self-explanatory. Can you elaborate on this a little?

**Author Response:**

On page 12, second paragraph we elaborated on this like follows: This result is in line with both the gateway hypothesis, which assumes a hierarchy in drug use with the use of legal substances followed by cannabis and “hard” drugs, and the common liability to addiction model, emphasizing the importance of socialisation and personality characteristics. However, beyond the variables discussed in these models, health-related variables, particularly depressiveness might influence the onset of drug use.

21. “Psychopathological factors, such as a previous history of depression symptoms, have been commonly studied as risk factor of drug use [7];...”: This sentence is misleading, as the cited study suggests depressive disorders to be a consequence rather than a risk factor of cannabis use.

**Author Response:**

Thanks. As mentioned by the Reviewer, the cited study considered depressive disorders as a consequence rather than a risk factor of cannabis use. Therefore, this study was removed and the following citation was inserted (page 3, second paragraph):


Tables:

22. Control group in table 1 and 2: Is it possible that this group contains subjects who have initiated SU after baseline but stopped within the following 3 months are not captured by the follow-up assessment? If so, this problem should be discussed!

**Author Response:**

The limitations section (page 14, second paragraph) was extended and also includes this limitation raised by the reviewer (point 3):

“The limitations of the study are (1) that only men were included, as only young men have to visit the army recruitment centres, and that the results could not be generalised to young women, (2) that the participants were observed for a relatively short time period, as they were reassessed only once after 15 months, (3) that there is a period of 3 months that is not covered by the assessments because the follow-up assessment takes into account only the preceding 12 months, (4) that all data rely on self-report without biochemical verification or inclusion of genetic risk factors, and (5) that statistical power was low for some of the examined predictor variables, particularly within the multivariate models predicting onset of drug use other than cannabis.”
Reviewer 2: Peter Gates
Reviewer’s report:

Major Compulsory Revisions

Abstract:
Need to describe how the samples of participants were obtained (C-SURF) and the ‘n’ at follow-up

Author Response:
Thanks. This information is now included in the Abstract:
“The data were gathered within the Cohort Study on Substance Use Risk Factors (C-SURF)...”
“... Onset of cannabis and other drug use were assessed at 15-months follow-up. Samples of 2,774 and 4,254 individuals without baseline lifetime use of cannabis and other drugs, respectively, and available follow-up data were used for the prediction models.”

Background:
- A definition of “early” and “late” onset to substance use is missing and why the distinction is important?

Author Response:
“Late onset of use” has been defined as “onset of use at adulthood” in third paragraph of the Background section (page 3). The third paragraph in the Background section has also been rewritten in order to explain and clarify why the distinction between both concepts is important.

- It is not clear why a sample of only young males was chosen and not a wider sample. It appears that the main reason for this choice was limitations of the data rather than purposeful selection.

Author Response:
In the limitations section (page 14, second paragraph) we added that one limitations of the study is that only men were included, as only young men have to visit the army recruitment centres:
“The limitations of the study are (1) that only men were included, as only young men have to visit the army recruitment centres, and that the results could not be generalised to young women, (2) ...”

Methods:
- What were the circumstances of the follow-up interview? Who conducted this?
Was it the “three army recruitment centres”?

Author Response:
In the section “Participants” on pages 5 and 6 we described the circumstances of the assessments.
“Of the 13,245 conscripts informed about the study (87.9%), 7,563 individuals (57.1%) gave written consent to participate and 5,990 individuals (79.2%) completed the baseline questionnaire. This has been sent out to them privately, two weeks after recruitment centre visits. The follow-up
questionnaire was sent out to the participants approximately 15 months after the baseline questionnaire.”

- How did the final sample come to be pooled from the three centres? Any differences?

Author Response:
Although the study is not fully representative, it covers mainly rural and mainly urban cantons, cantons in the north, south, west and east of Switzerland, and the two main linguistic regions. There may be differences between individuals enrolled in different centers, but these differences reflect differences across Switzerland. The total sample was therefore analysed as a sample reflecting the two main linguistic regions. We explain that on page 5 under the heading “enrolment procedures”.

- If not all, but “virtually all” Swedish males were selected, then who was not?
Participants:

Author Response:
Ineligible are those who do not have to go through army procedures, e.g. being diagnosed for severe and chronic mental and physical disablement (e.g. with trisomy 21, being blind or paraplegic). According to information from the Army this concerns less than 3 % of the Swiss male population at this age. This is now explained in the revised version on page 5 under the subheading “enrolment procedures”.

- How could the non-inclusions be said to be random when they included those who were dropped due to illness?

Author Response:
The referee is right here, although this were mainly common colds, Substance use could have an effect on illness. The main argument for not influencing the study findings is that these people would have to come to the recruitment center again, and would be included then. This is now stated in the revised version under the subheading “participants”.

- The percentages provided refer to different totals and need further explanation

Author Response:
We reformulated the following sentences in order to avoid confusion due to percentages of different totals (page 6, section “participants”):
“Of the 13,245 conscripts informed about the study, 7,563 individuals (57.1%) gave written consent to participate. Of these, 5,990 individuals (79.2%) completed the baseline questionnaire.”
Measures:

- Many different measures are described and some cut-off points, with no information on validity or reliability

**Author Response:**
The C-SURF study aimed at considering all major risk factors for substance use. However, due to the length of the baseline and follow-up questionnaire, primarily short versions of the instruments were preferred given that they had good psychometric properties.

A full list of instruments and corresponding references can be found on [www.c-surf.ch](http://www.c-surf.ch). Instruments were chosen based on recommendation of the World Health Organization, because they have been shown to be valid in different languages, or based on literature research appeared to be the most often used.

- No information on the follow-up interview is provided including the drop out and measures

**Author Response:**
In the section “Participants” on page 6 we included additional information on the follow-up assessment measures and on the drop out at follow-up:

“The follow-up questionnaire was sent out to the participants approximately 15 months after the baseline questionnaire. It consisted of similar questions as the baseline questionnaire addressing the domains “sociodemography”, “health”, “social context”, “substance use”, “personality”, and “sexuality”. Additionally, the follow-up assessment included questions on the attendance of military training school.”

“...For the analysis of the late onset of drug use other than cannabis, we excluded 1,017 of the 5,990 individuals (17.0%) due to a lifetime use of illegal drugs other than cannabis at baseline and an additional 719 individuals (12.0%) with missing follow-up data.”

“...For the analysis of the late onset of drug use other than cannabis, we excluded 1,017 of the 5,990 individuals (17.0%) due to a lifetime use of illegal drugs other than cannabis at baseline and an additional 719 individuals (12.0%) with missing follow-up data.”

Analysis:

- The importance of this study appears to hinge on the inclusion of many different predictors into the one study. I am not completely familiar with the statistical methods, however; given how many analyses were conducted I would assume that Bon Ferroni corrections would apply? In the least, the authors should describe how they addressed the number of univariate analyses beyond only including the significant factors to “account for suppressor effects” as this is not
sufficient.

**Author Response:**
Yes, a major strength of the study is the comprehensive set of predictors.
For the selection of the most important predictors we used backward and forward elimination using hierarchical logistic stepwise regressions.
Based on statistical textbooks, e.g., Linear Models with R from Julian J. Faraway (Taylor and Francis).
No alpha level adjustment is necessary when running these procedures. Sometimes alpha-cut-offs higher than 5% are recommended (see below).

Citation from the textbooks, Linear Models with R from Julian J. Faraway (Taylor and Francis)
“Backward Elimination
This is the simplest of all variable selection procedures and can be easily implemented without special software. In situations where there is a complex hierarchy, backward elimination can be run manually while taking account of what variables are eligible for removal.
1. Start with all the predictors in the model
2. Remove the predictor with highest p-value greater than alpha_crit
3. Refit the model and go to 2
4. Stop when all p-values are less than alpha_crit.
The alpha_crit is sometimes called the .p-to-remove. and does not have to be 5%. If prediction performance is the goal, then a 15-20% cut-off may work best.”

- Is the power of analyses sufficient given the great difference between groups with minimal drug users (I note some cases with ‘n’ less than 10 for example)?

**Author Response:**
Although the statistical power is sufficient for most predictor variables, statistical power is low for single of the examined variables, particularly in the multivariate model predicting onset of drug use other than cannabis. We mentioned this in the limitations section on page 14:

“The limitations of the study are..., and (5) that statistical power was low for some of the examined predictor variables, particularly within the multivariate models predicting onset of drug use other than cannabis.”

Discussion:
- The authors do very little other than repeat the results and show how they were in line with previous study and brief mention of gateway hypotheses. The importance of the study is lost unless the authors offer some information on the implications of their findings.
Author Response:
The discussion and conclusions sections were extended to include more information on how the results fit to the gateway and the common liability to addiction model (2nd paragraph of the Discussion and Conclusions).

- The authors summarise their findings by suggesting topics for screening instruments. Is there nothing more the study findings can offer?

Author Response:
The Conclusions were extended as follows
“The results of this study provide evidence for the gateway hypothesis and the common liability to addiction model and point on further variables, not addressed in these models that might influence the onset of drug use. Furthermore, they help to identify male young adults for whom preventive measures for cannabis or other drug use are most appropriate and might help to develop screening instruments for the identification of male young adults at risk for cannabis and other drug use.”

Minor Essential Revisions
Background:
- The first paragraph includes a few sentences that leave the readers to make assumptions that should be clarified. First it is not described where the 230 million individuals are from, and the information that is cited does not state current use as is insinuated but past year use. Second, it is not clear what “manner” of use leads to health problems.

Author Response:
The first paragraph has been rewritten in order to clarify this issue.

- The second paragraph switches between associations between factors and drug use (current?), onset to use, subsequent problems and back to onset of use, and is a bit haphazard. I would suggest a re-write.

Author Response:
The second paragraph has been rewritten in order to clarify that the information of the paragraph refers to the onset and escalation of drug use.

- The third paragraph is more important and I would suggest moving this to earlier in the Background. The sentences, “Most studies underline the early-onset drug use concept” means, and “…period of risk initiation can be extended further into adulthood…” do not read well.

Author Response:
As suggested, the sentences “Most studies underline the early-onset drug use concept” and “…period of risk initiation can be extended further into adulthood…” have been rewritten.
Reviewer 3: Monique Delforterie

Major Compulsory Revisions

1. The major limitation is that the study lacks an explicit theoretical foundation and explicit theory-based hypotheses. The way it is described now, it looks like a dataset of male young adults available to the researchers was used, including different variables which by chance could be grouped into various categories. Below are some suggestions for improvements:

Author Response:
The C-SURF study aimed at considering all major risk factors for substance use. The variables were not included by chance. The strength of the study is its comprehensive set of predictors from various domains. Therefore, we chose a bottom-up rather than a top-down approach in order to explore the most important variables predictive for drug onset and discussed how the results fit with the most important models in this field the gateway hypothesis and the common liability to addiction model.

The aims of the study were reformulated in the last paragraph of the Background:
“Our longitudinal study aimed at investigating the association of a comprehensive set of major risk factors for substance use derived from previous studies with the onset of cannabis and the onset of other illegal drug use separately in male young adults. The results of the study might (1) help to identify individuals for whom preventive measures for cannabis or illegal drug use are most appropriate and (2) to explore how far the current models of cannabis and other illegal drug use and their hypothesised risk factors are in line with the resulting prediction models.”

The Discussion and Conclusions were extended to include more information on how the results fit to the gateway and the common liability to addiction model (2nd paragraph of the Discussion and Conclusions).

2. From the Background, it is not clear why it is important that we not only look at young initiating substance users, but also at young adult initiators. Do they have the same outcome in later life, for example in terms of mental health or education? Does it interfere with work, or with social relations?

Author Response:
The third paragraph of the Background, that has been rewritten, and addresses why it is important to look at young adult initiators.

3. As said, the study lacks an explicit theoretical foundation. The gateway hypothesis explains the use from licit to illicit drugs, but is less suitable to explain the relation with demographic variables, parenting, personality. The common liability to addiction model seems to be more useful to explain the research question, however, a stronger background on this model is needed.
Author Response:
We added additional information on the common liability to addiction model in the fourth paragraph of the Background section.

4. The description of the variables that were used, should be given more attention in the Background. Why were these specific variables included, how do you expect them to affect cannabis and illicit drug use, and what was found by previous articles (5, 11, 13)?

Author Response:
As noted above, the study aimed at considering all major risk factors for substance use. We integrated more information on previous studies, particularly longitudinal, prospective studies in the Background section (second and third paragraph).

5. Provide a clear rationale for the selected categories and the selected variables in those categories. Some variables in the category Personality do not seem to fit the description of personality. I would suggest to exclude peer pressure from this category, and include this into the category Social context. Adult attention deficit syndrome and anti-social personality disorder would be more suitable for the Health category. Include a rationale for including these into the personality category, or switch them to the appropriate categories.

Author Response:
Thanks. Peer pressure was switched to the category “social context”. Furthermore, we switched “adult attention deficit syndrome” and “anti-social personality disorders” to the category “health”. Based on these changes, we recalculated the multivariate models (Tables 3 and 4) however the results of the final multivariate models remained similar as in the previous version.

Minor Essential Revisions
Background
1. It is not clear why you would expect different risk factors for young adults than for (young) adolescents.

Author Response:
This third paragraph of the Background section was extended to address this issue.

Method
2. The construct parental monitoring implies that parents are actively involved to receive knowledge on their children’s whereabouts. However, in the present study, parental monitoring is measured as parental knowledge. This should be described accordingly (see Stattin and Kerr, 2000 and Kerr and Stattin, 2000).

Author Response:
We thank the referee for this remark. We explained the difference between parental monitoring and parental knowledge about whereabouts in the Method section “social context”. And we changed the MS accordingly from parental monitoring to “parental knowledge of peers and the whereabouts” after the explanation.

3. The description of the substance use variables should be made clearer. From the table, it looks like a variable with multiple groups was used (e.g., (1) no use, (2) low nicotine dependence, (3) moderate-high nicotine dependence), but this is not clear from the description. Clearly specify in which groups participants could be divided.

Author Response:
The section Predictor variables/Substance Use was extended to include on which basis which classifications were made.

4. Parental regulation and parental monitoring were both assessed at age 15. Why was that age used, and how could it have affected results?

Author Response:
Parental rule setting and parental monitoring was asked at around age 15, because this is the time when peer influences become stronger, and particularly meeting with friends without the participation of parents increase (see also Coleman, J. C. (4th ed.) (2011). The nature of adolescence. London and New York: Routledge, Psychology Press).

For example, the Health Behaviour of School Aged Children showed across 41 European countries that peer influences such as being four or more days per week out with friends, increases strongly between the age 11 to 15. This has been explained now in the “social context” part of the method section.

We agree that this is somewhat arbitrary an earlier time point could have been chosen (e.g. 13), and socializing with friends will increase furthermore, but parental influences will also increase. We choose 15 years as a time point, where clear increases of time out with friends without parent s being present increases, but also to avoid recall biases when going back too far in the past.

5. The result section lacks statistical information. I would suggest to include the R2 of the total model, at the very least.

Author Response:
The R² of the overall models were integrated into the results section. To avoid redundancy with the tables, we did not include more statistical information into the results section.
Discussion

6. A more critical examination of the study is needed. How reliable is self-report in this population? What could be the downside of the low number of written consent (57%)? What about generalizability, also to a female population?

**Author Response:**
*In the discussion section, we added the limitation that all data rely on self-report (penultimate paragraph of the discussion section) and that only men were included, as only young men have to visit the army recruitment centres, and that the results could not be generalized to young women.*

7. The attendance of military training seems to get too much attention in the discussion, as this was merely a control variable to be clear on the generalizability of this sample.

**Author Response:**
*We maintained two short sentences on this issue (paragraph above the Limitations in the Discussion). From our point of view this is appropriate. However, we deleted this point from the list of main findings at the beginning of the discussion.*

8. The sentence “Previous research also revealed that cannabis use is a common behaviour among young adults who are experiencing unfavourable employment conditions or socioeconomic disadvantages [33]” is unrelated to the rest of the discussion, and to the results in the present study. I would suggest to exclude this sentence, or expand on its applicability in this study.

**Author Response:**
*This sentence refers to the variable “means of subsistence” that has been related to the onset of cannabis use. In order to understand its meaning, the sentence has been written as follows: “Previous research also revealed that cannabis use is a common behaviour among young adults who have problems in their means of subsistence”.*

9. The inclusion of both cannabis and other illicit drug use in the present study is interesting and important, however, the combination of risk factors found for both cannabis and illicit substance use should be discussed in more detail.

**Author Response:**
As suggested, the combination of risk factors found for both cannabis and other drug use has been discussed in more detail in the fourth paragraph in the Discussion section (second paragraph on page 13).

10. The common liability model proposes that using both licit and illicit drugs may be because of the influence of a common liability. What would the researchers conclude from their study, which common liabilities can explain both cannabis and illicit drug use in young adulthood? Additionally, a genetic vulnerability is missing in the present study, which should be included in the limitations.

**Author Response:**
Within the 4th paragraph of the discussion section (second paragraph on page 13) we added “Some variables related to cannabis were also predictive of the onset of drug use other than cannabis, including depressiveness, religiosity, parental monitoring, anxiety, and sensation-seeking. These variables present promising candidates to be included into a common liability of addiction model.”
In the limitations section we included ...“(4) that all data rely on self-report without biochemical verification or inclusion of genetic risk factors ...

Discretionary Revisions
1. For a better comprehension of the direction of the relations, it should be made clearer throughout the different sections of the article that this is a longitudinal study.

**Author Response:**
Thanks, we added that this is a longitudinal study in different sections (Abstract, Background, Discussion) and the title.
Reviewer 4: Hrefna Palsdottir

1. Discretionary Revisions

- The word “investigate” is often used, it could be better to use “explore” or “study”

Author Response:
Thanks. We replaced the word investigate as suggested.

- Under Abstract (8th paragraph) – “baseline lifetime use” you could be a bit clearer in what you mean by that, describe it better.

Author Response:
Thanks. This sentence was rewritten as follows:
“Samples of 2,774 and 4,254 individuals who indicated at baseline that they have not used cannabis and other drugs, respectively, in their life and who provided follow-up data were used for the prediction models.”

2. Minor Essential Revisions:

- The description of “sample” is unclear. The chapter called: “Participants” is mostly describing the “sample” and the chapter called: “Enrolment Procedure” is mostly describing the participants.

Author Response:
We reformulated the following sentences in order to avoid confusion due to percentages of different totals (page 6, section “participants”):
“Of the 13,245 conscripts informed about the study, 7,563 individuals (57.1%) gave written consent to participate. Of these, 5,990 individuals (79.2%) completed the baseline questionnaire.”

- Under the chapter: “Measures” - The variables “health” and “personality” need a clearer description on the scales being used in accordance to other scales used.

Author Response:
Peer pressure was switched to the category “social context”. Furthermore, we switched “adult attention deficit syndrome” and “anti-social personality disorders” to the category “health”. Based on these changes, we recalculated the multivariate models (Tables 3 and 4) however the results of the final multivariate models remained similar as in the previous version.
• It could be clearer to describe it better why you need to assess or why it is important whether participants have not started, started, finished or discontinued military training, in the chapter “Attendance of military training school”.

Author Response:
Primarily, military attendance was considered as a potential confounder that potentially might have influenced generalizability of the data.

3. Major Compulsory Revisions
• The research question is missing or you could have the goal of the study a bit clearer.

Author Response:
The research aims were reformulated in the last paragraph of the Introduction:
“Our longitudinal study aimed at investigating the association of a comprehensive set of major risk factors for substance use derived from previous studies with the onset of cannabis and the onset of other illegal drug use separately in male young adults. The results of the study might (1) help to identify individuals for whom preventive measures for cannabis or illegal drug use are most appropriate and (2) to explore how far the current models of cannabis and other illegal drug use and their hypothesised risk factors are in line with the resulting prediction models.”

• The interpretation is clear and the relevance of the results are discussed. The chapter on limitations is on the other hand rather weak. Could for example “self report” be a limitation to the research? Or environmental changes? The strength of the study is not mentioned either. For example you have a great access to the young men, who are representative of the young men living in in Switzerland.

Author Response:
Thanks. The section on the limitations was extended and the strengths of the study were added in a separate sentence as follows:

“The limitations of the study are (1) that only men were included, as only young men have to visit the army recruitment centres, and that the results could not be generalized to young women, (2) that the participants were observed for a relatively short time period, as they were reassessed only once after 15 months (3) that there is a period of 3 months that is not covered by the assessments because the follow-up assessment takes into account only the preceding 12 months, (4) that all data rely on self-report without biochemical verification or inclusion of genetic risk factors and (5) that statistical power was low for some of the examined predictor variables, particularly within the multivariate models predicting onset of drug use other than cannabis.
The strengths of the study include that the analyses are based on a relatively large dataset of an age-homogeneous group and the comprehensiveness of the predictor variables investigated.”
• The conclusion drawn from the study points only to the benefits of the study or implications for practice / the findings of the study – for example why it is important to screen for these young male adults - are missing. The conclusion is supposed to be valid and result from the data shown. It could be useful to look at more references to other relevant work to strengthen the conclusion.

**Author Response:**

The Conclusions were rewritten as follows:

“The results of this study provide evidence for the gateway hypothesis and the common liability to addiction model and point on further variables, not addressed in these models that might influence the onset of drug use. Furthermore, the results may help to identify male young adults for whom preventive measures for cannabis or other drug use are most appropriate and to develop screening instruments for the identification of male young adults at risk for cannabis and other drug use.”

• The chapter “Participants” is a bit unclear and confusing. It could be better to describe the process in a table instead of a full-text. It would also be clearer to have the total participants in each category in a table.

**Author Response:**

The Participants section on pages 5/6 has been modified and should be clearer now.

• What is missing is to mention (and describe better) the self-reported questionnaires, where did the young men fill them out, did they all do it at the same time and to describe the booklet. You could also mention how the 15th months follow-up was implemented.

**Author Response:**

Within the Participants section on pages 5/6 we added the setting where the participants filled out the questionnaires and how they were invited to fill out the follow-up:

“...Of these, 5,990 individuals (79.2%) completed the baseline questionnaire. These have been sent out to them privately, two weeks after recruitment centre visits. The follow-up questionnaire was sent out to the participants approximately 15 months after the baseline questionnaire. It consisted of similar questions as the baseline questionnaire addressing the domains “sociodemography”, “health”, “social context”, “substance use”, “personality”, and “sexuality”.”