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ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>Childhood academic ability in relation to cigarette, alcohol and cannabis use from adolescence into early adulthood: Longitudinal Study of Young People in England (LSYPE)</th>
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<tr>
<td>AUTHORS</td>
<td>Williams, James; Hagger-Johnson, Gareth</td>
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GENERAL COMMENTS

This is a potentially interesting longitudinal study of childhood academic ability and substance use across adolescence, based on data from a relatively large cohort study in England. The authors find high ability is associated with a reduced risk for persistent smoking, whereas opposite associations are seen with the frequency of alcohol use and cannabis use. The results may have value in clarifying the long-term associations between academic ability and the development of substance use, where earlier studies have resulted in some inconsistency. However, there are some issues with the study methods and analyses which need to be clarified. The following specific points may be considered.

(1) The authors refer to Figure 1, but at least my copy of the submitted manuscript didn’t include a figure. However, a graphical explanation of the rather complex two-stage sampling should be provided, together with exact numbers (targeted and participated) for each stage.

(2) The categorizations used for the variables for smoking, drinking and cannabis use should be justified better. These are not self-evident decisions, and they are likely to influence the results.

(3) Please describe what exactly is meant by “independent schools” (p. 10) and provide data on proportions of pupils in independent schools in the descriptives.

(4) It is not clear why Table 2 is included. It is not motivated in the analysis description, and the main analysis with multinomial logistic regression gives all the relevant results. Furthermore, the comparison with the whole sample population seems odd because it ignores the fact that those who report “frequent alcohol drinking” or cannabis use at ages 18-20 belong to the subpopulation who were not lost to follow-up at those ages. Thus, the correct comparison should be with those reporting no alcohol/cannabis use at those ages (as is done in the logistic model).
In Table 3 (and throughout the manuscript), the terms “frequent use” and “regular use” are used inconsistently. Please select one and stick to it. Currently, the text is unclear and difficult to follow.

Please state clearly the reference categories used in the multinomial analyses in Table 3. Also, in the footnote, p<0.05 should be p>0.05.

On p. 11, please note that a difference between a significant coefficient and a non-significant coefficient is not necessarily itself significant. Thus, the suggested non-linear association between academic ability and cannabis use may not be a real finding (and in fact, the 95% CIs are widely overlapping).

The authors state that hazardous alcohol use will be studied (and refer to such an analysis on p. 12) but no results are given. Please provide these results.

There are several additional sensitivity analysis that would be useful. First, showing the associations between ability and each individual substance use measure would be useful (as a polychoric correlation table, for example) to see that the results are robust and not driven by the complex substance use variable combinations. Second, in addition to tertiles of academic ability, a more fine-grained categorization (e.g. quintiles) could be used. Third, it would be interesting to know if there were any indications of sex differences in the associations. In that case, separate analyses for boys and girls would be useful. Fourth, specific associations with performance in the different tests of the Key Stage 2 might shed light on the nature of the observed associations – are they general or driven e.g. by verbal ability as has been suggested in some previous studies.

In the discussion, potential explanations for the inconsistent results for ability and alcohol use in the literature and in this study should be provided. For example, are there period/cohort effects such that the role cognitive ability plays with regard to substance use might have changed over time? Or, are there cultural/societal differences which might explain the differences?

It should also be noted in the discussion that in contrast to frequency of alcohol/substance use, the association between ability and alcohol/substance abuse (or problematic use) is much more consistent: lower ability has been systematically found to predict more problems. See for example recent studies from the Swedish conscript cohorts.

The purely observational study design is unable to shed light on the underlying mechanisms giving rise to the observed associations (e.g. causality vs. confounding by shared risk factors such as genetic influences). This should be acknowledged as a major limitation.

The aim of present study was to assess how academic ability at the group.bmj.com on August 6, 2017 - Published by http://bmjopen.bmj.com/Downloaded from
age of 11 is related to the onset and persistence of smoking, drinking alcohol and using cannabis. In several waves they assessed substance abuse in large sample of students, starting at the age of 13/14. A higher academic ability is found to be associated with a lower rate of smoking but with a higher uptake rate and persistence of drinking and using cannabis. And although I found the results interesting, I have some questions regarding the design and the analyses of the data.

Their objective is to look both at the onset and at the persistence of use. Most of the results however relate to occasionally and persistent use, and not to the onset of use. Alcohol for example is categorized into regular and non-regular drinking (including non-drinking) and therefore the onset of drinking was not taking into account.

It was a two-stage stratification. First schools were selected and then students. Did school play a role in the analyses? In addition, they describe the characteristics of the independent schools separately, but the reason for that is not really mentioned. Only in the discussion the authors state, that they only had academic data for one third of these students. They refer to a study in Sweden in which was found that a lower academic ability at the age of 18-21 was associated with male drinking. In short might by academic ability change over time? And could this play a role in these found differences? In line with these results in Sweden, were there any gender differences in the onset and persistence? Looking at the percentages there seem to be some gender variations.

Next in the discussion the authors state that a limitation of their study is that there is no data on quantity of alcohol. But in the methods section they describe they also included the frequency of drunkenness. I am not sure however whether this variable was actually used in the analyses.

The authors have decided to analyse the data separately for the younger and older group. But history of alcohol or cannabis use in the older group seems not to be included in the analyses on late alcohol or cannabis use. I therefore wondered why they did not choose longitudinal methods to analyse their data, to explore for example whether there are trajectories of cannabis use and alcohol use. It would be interesting to know whether there is a group that starts early and persist during all waves, a group that starts late, a group that starts early but does not persist……. Related to academic abilities it could provide more insight in whether there are academic variations in pathways of substance use.

They categorized academic ability score in three groups, using tertiles, but does that provide a valid reflection of ability? Are scores normally distributed? And how do they compare to the distribution of scores in the total sample (including the ones lost to follow-up) or to all children aged 11.

They also included drunkenness, but it is unclear how that variable was taken into account in the analyses.

Table 1 includes the percentage of early persistent users. I suggest to also including the % of occasional users and I think it would be useful to also present the % of later persistent and later occasional
users.

Table 2. Suggestion to add a column for the means and % in the non-user group, one for alcohol and one for cannabis.

In the text the authors refer to figure 1, but it was not attached to this manuscript.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1

R1.1. The authors refer to Figure 1, but at least my copy of the submitted manuscript didn’t include a figure. However, a graphical explanation of the rather complex two-stage sampling should be provided, together with exact numbers (targeted and participated) for each stage.

Response: As requested, Figure 1 has now been attached and an appendix added (Appendix 1), which details the response rates and sample sizes at each stage of the study. An explanation of the two-stage sampling process has been added to the manuscript (pg 6).

R.1.2. The categorizations used for the variables for smoking, drinking and cannabis use should be justified better. These are not self-evident decisions, and they are likely to influence the results.

Response: We have repeated the analyses with higher cut-off points (e.g. regular smokers previously defined as “I sometimes smoke cigarettes now but I don’t smoke as many as one a week” now defined as “I usually smoke between one and six cigarettes a week” etc.) and found that the associations were slightly stronger as expected, but with little change to overall patterns of results or conclusions drawn. This is mentioned in the revision (pg 13).

R.1.3. Please describe what exactly is meant by “independent schools” (p. 10) and provide data on proportions of pupils in independent schools in the descriptives.

Response: The definition of independent schools has been clarified as “fee-paying” schools, as opposed to maintained schools in the public domain. The proportion of pupils from independent schools has been clarified as “3.36% (530/15,770) of the total study population and 1.67% of the analytic sample (101/6,059)” (pg 10).

R.1.4. It is not clear why Table 2 is included. It is not motivated in the analysis description, and the main analysis with multinomial logistic regression gives all the relevant results. Furthermore, the comparison with the whole sample population seems odd because it ignores the fact that those who report “frequent alcohol drinking” or cannabis use at ages 18-20 belong to the subpopulation who were not lost to follow-up at those ages. Thus, the correct comparison should be with those reporting no alcohol/cannabis use at those ages (as is done in the logistic model).

Response: We felt it helpful to describe the association between the study variables and patterns of substance use in later adolescence without adjustment at baseline, so that readers could appraise the confounding structures in the data. These help justify the need for additional adjustment in the main multinomial results. As a compromise, we have now moved this table to the appendix since Table 1 has a similar purpose.

R.1.5. In Table 3 (and throughout the manuscript), the terms “frequent use” and “regular use” are used inconsistently. Please select one and stick to it. Currently, the text is unclear and difficult to follow.

Response: As requested, we have opted for the term ‘regular use’ and have modified the manuscript to reflect this. We have also clarified this term as “repeated use of a substance over a period of 12 months” (pg 5). The use of the term “frequency of use” in the introduction when referring to the negative outcomes related to cannabis use (pg 5) refers to the original studies’ ability to measure
cannabis use quantitatively.

R.1.6. Please state clearly the reference categories used in the multinomial analyses in Table 3. Also, in the footnote, p<0.05 should be p>0.05.
Response: The reference category is 'low' for both outcomes, that is, high vs. low and med vs. low. The footnotes of the tables have been edited to read p>0.05.

R.1.7. On p. 11, please note that a difference between a significant coefficient and a non-significant coefficient is not necessarily itself significant. Thus, the suggested non-linear association between academic ability and cannabis use may not be a real finding (and in fact, the 95% CIs are widely overlapping).
Response: The manuscript has been edited to emphasise the fact that "caution must be taken when interpreting" (pg 11) the possible non-linear association due to the overlapping confidence intervals.

R.1.8. The authors state that hazardous alcohol use will be studied (and refer to such an analysis on p. 12) but no results are given. Please provide these results.
Response: These results have now been included in the manuscript (p. 13), along with a graphical representation of the data as Appendix 6.

R.1.9. There are several additional sensitivity analysis that would be useful. First, showing the associations between ability and each individual substance use measure would be useful (as a polychoric correlation table, for example) to see that the results are robust and not driven by the complex substance use variable combinations. Second, in addition to tertiles of academic ability, a more fine-grained categorization (e.g. quintiles) could be used. Third, it would be interesting to know if there were any indications of sex differences in the associations. In that case, separate analyses for boys and girls would be useful. Fourth, specific associations with performance in the different tests of the Key Stage 2 might shed light on the nature of the observed associations – are they general or driven e.g. by verbal ability as has been suggested in some previous studies.
Response: The association between ability and each substance use measure is already shown in the descriptive table, but we additionally checked that results were not influenced by other substance use combinations, by additionally controlling for the other two behaviours in each health behaviour model. In our view this is preferable to a polychoric correlation matrix, which would only show the bivariate association between each pair of variables and mask potentially complex confounding structures in the data.
The reason tertiles were originally selected was for ease of understanding for the target audience of clinicians and policy makers. We originally checked for dose-response associations using ability on a continuous scale (KS2 score) and associations were nearly always perfectly linear, which means that using tertiles is justified. Results are similar when using quintiles, with only slightly stronger associations, which add little to the analysis and interpretation. We have now added a note to the manuscript to this effect (p. 9).
We tested for effect modification by sex and the results were not statistically significant (p > 0.05) so males and females were analysed together, treating sex as a covariate. This is now detailed in the methods section of the manuscript (p. 8). Unfortunately, subscales of KS2 results (e.g. verbal ability in English) were not available within the first author’s data access agreement from UK Data Service. We decided to use the average KS2 score as opposed to the individual subject scores due to a previous study's finding that average KS2 acted as a good proxy for childhood intelligence. We agree with the reviewer however, and so have emphasised in the discussion section that subscales should be considered in future research (p. 16).

R.1.10. In the discussion, potential explanations for the inconsistent results for ability and alcohol use in the literature and in this study should be provided. For example, are there period/cohort effects such that the role cognitive ability plays with regard to substance use might have changed over time?
Or, are there cultural/societal differences which might explain the differences?
Response: We agree that age/period/cohort effects are likely to cause inconsistent results in the literature, but since LSYPE is an age-narrow birth cohort, it cannot be used to separate age/period/cohort. This is acknowledged as a major limitation in the discussion section, with reference to the wider literature (p. 16). In the near future, the second cohort (LSYPE2) can be used to make comparisons between two cohorts.

R.1.11. It should also be noted in the discussion that in contrast to frequency of alcohol/substance use, the association between ability and alcohol/substance abuse (or problematic use) is much more consistent: lower ability has been systematically found to predict more problems. See for example recent studies from the Swedish conscript cohorts.
Response: The manuscript has now been edited to include this important point of consideration, including a new reference to the relevant literature: “It should not be assumed that children with low academic ability are at higher risk for substance use, despite the fact that this group of pupils are more likely to develop adverse health outcomes and misuse of substances.[27, 40]” (pg 15).

R.1.12. The purely observational study design is unable to shed light on the underlying mechanisms giving rise to the observed associations (e.g. causality vs. confounding by shared risk factors such as genetic influences). This should be acknowledged as a major limitation.
Response: As requested, the discussion now includes a paragraph acknowledging this limitation of the study: “A major limitation of this paper is the purely observational design of the study. As outlined above, there are many factors that may play a role in the complex relationship between childhood academic ability and adolescent substance use, and it is not possible to conclusively shed light on the underlying mechanisms responsible for the results seen here” (pg 15).

Reviewer 2

R.2.1. Their objective is to look both at the onset and at the persistence of use. Most of the results however relate to occasionally and persistent use, and not to the onset of use. Alcohol for example is categorized into regular and non-regular drinking (including non-drinking) and therefore the onset of drinking was not taking into account.
Response: Onset was taken into account in the sense that usage was defined as a regular/frequent pattern. The results capture the onset of the first pattern of usage that meets this definition.

R.2.2. It was a two-stage stratification. First schools were selected and then students. Did school play a role in the analyses? In addition, they describe the characteristics of the independent schools separately, but the reason for that is not really mentioned. Only in the discussion the authors state, that they only had academic data for one third of these students.
Response: We adjusted for variance at the school level, but did not include school-level covariates (few are available since schools are not identifiable). We also used sample weights which adjust for over-sampling (e.g. of fee-paying schools). We described the characteristics of independent schools separately for another reason – that systematic bias is introduced because they tend not to have KS2 data. Design/sampling issues and bias resulting from KS2 not being universally available are two separate issues – we apologise for not making this clearer, and have revised the methods/results sections accordingly (p. 6 and 10).

R.2.3. They refer to a study in Sweden in which was found that a lower academic ability at the age of 18-21 was associated with male drinking. In short might by academic ability change over time? And could this play a role in these found differences? In line with these results in Sweden, were there any gender differences in the onset and persistence? Looking at the percentages there seem to be some gender variations.
Response: We checked for effect modification of the associations by sex and found no evidence in
this cohort that sex was a modifier (all p values > 0.05). For this reason, males and females are combined in the main analysis and sex is treated as a covariate.

R.2.4. Next in the discussion the authors state that a limitation of their study is that there is no data on quantity of alcohol. But in the methods section they describe they also included the frequency of drunkenness. I am not sure however whether this variable was actually used in the analyses.

Response: This variable of hazardous drinking was derived by combining regularity of drinking with drinking alcohol to the point of drunkenness. Individuals who were calculated to get drunk on average once per week were deemed to exhibit hazardous levels of alcohol consumption. A comparison between those exhibiting hazardous vs. non-hazardous alcohol drinking has now been included as Appendix 6.

R.2.5. The authors have decided to analyse the data separately for the younger and older group. But history of alcohol or cannabis use in the older group seems not to be included in the analyses on late alcohol or cannabis use. I therefore wondered why they did not choose longitudinal methods to analyse their data, to explore for example whether there are trajectories of cannabis use and alcohol use. It would be interesting to know whether there is a group that starts early and persist during all waves, a group that starts late, a group that starts early but does not persist……. Related to academic abilities it could provide more insight in whether there are academic variations in pathways of substance use.

Response: To clarify, the same group of pupils is being followed over time. There are a relatively small number of possible patterns of onset and persistence, since pupils can either be not using or using a substance at each wave. We did use longitudinal methods to analyse these patterns over time, since the later time period captures persistence of use over time. Onset and persistence are longitudinal outcome measures. Although more complex techniques (e.g. growth mixture modelling) are available, we don’t feel they would add much substantively different from the simpler approach used here, particularly for clinicians and policy makers.

R.2.6. They categorized academic ability score in three groups, using tertiles, but does that provide a valid reflection of ability? Are scores normally distributed? And how do they compare to the distribution of scores in the total sample (including the ones lost to follow-up) or to all children aged 11.

Response: See response to reviewer 1 above – we initially used continuous KS2 score which shows associations are linear, supporting the use of tertiles. Results were similar using quintiles. KS2 scores are normally distributed. The mean KS2 score of the analytic sample was 27.86 vs. 26.09 in the excluded population (which falls into the low ability tertile). In light of this, a note has been added to the results section regarding that results are slightly biased by higher ability pupils being more likely to end up in the analytic sample (p. 10)

R.2.7. They also included drunkenness, but it is unclear how that variable was taken into account in the analyses.

Response: See response to point R.2.4.

R.2.8. Table 1 includes the percentage of early persistent users. I suggest to also including the % of occasional users and I think it would be useful to also present the % of later persistent and later occasional users.

Response: As requested, Table 1 has been edited to include the percentages of occasional and persistent substance users in both early and later adolescence.

R.2.9. Table 2. suggestion to add a column for the means and % in the non-user group, one for alcohol and one for cannabis.

Response: As requested, Table 2 (now Appendix 2) has been edited to include a column detailing the
characteristics of the non-user group for both alcohol and cannabis use.

R.2.10. In the text the authors refer to figure 1, but it was not attached to this manuscript. Response: As requested, Figure 1 has now been attached.

GENERAL COMMENTS
The authors have responded to most of the comments. They conducted several additional analyses: such as exploring whether gender moderates the relation between substance abuse and ability, additional analyses with ability categorised in five groups..... These new analyses do not really change the results. One of the results I however find interesting and that is the one about hazardous alcohol use being more likely in low-ability students while regular alcohol use is more likely in the higher ability group.

Recently a Dutch study explored trends of multiple adverse health behaviours in a longitudinal cohort of adolescents: and they found that smoking often co-occured with other health risks behaviours, suggesting groups of students in which health risk clustered. (de Winter AF, Visser L, Verhulst FC, Vollebergh WA, Reijneveld SA. Longitudinal patterns and predictors of multiple health risk behaviors among adolescents: The TRAILS study. Prev Med. 2016 Mar;84:76-82.) Considering present data and the large sample it would be interesting to also look at the relation of ability and the co-occurrence of substances (or it might be input for another article). This would provide further information on the group of students with an increased risk of adverse outcomes of substance use.

I have no other comments.
Childhood academic ability in relation to cigarette, alcohol and cannabis use from adolescence into early adulthood: Longitudinal Study of Young People in England (LSYPE)

James Williams and Gareth Hagger-Johnson

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