

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Habitual alcohol consumption associated with reduced semen quality and changes in reproductive hormones; a cross-sectional study among 1,221 young Danish men
AUTHORS	Jensen, Tina; Gottschau, Mads; Madsen, Jens Otto; Andersson, Anna-Maria; Lassen, Tina; Skakkebaek, Niels; Swan, Shanna; Priskorn, Lærke; Juul, Anders; Jørgensen, Niels Erik

VERSION 1 - REVIEW

REVIEWER	Jaime Mendiola University of Murcia, Spain
REVIEW RETURNED	19-May-2014

GENERAL COMMENTS	<p>This is a very interesting study that highlights the potential importance of alcohol consumption on male reproductive parameters. It is a cross-sectional study investigating the association between alcohol consumption and semen quality and reproductive hormone levels in young men. This is the first paper looking at the effects of recent vs. regular alcohol exposure on those reproductive parameters.</p> <p>Specific Comments Page 21/28. Table 1: It seems there are some missing data on lines 23-26, in 5th-95th columns.</p> <p>There are more than a few results labelled by "data not shown", but might be of interest for the readers though. The authors could choose some of this information (the most relevant) and show it as supplementary tables as well.</p> <p>Overall, The design and the methodologies are satisfactory, with a well round analysis. The discussion presented is appropriate and consistent. The consulted references are updated and adequate. In my opinion, the paper presents novel data and is a well-organized manuscript that provides information that will be of interest to the readers of "BMJ Open".</p>
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REVIEWER	jpt Rhemrev Bronovo Hospital dept Obs/Gyn The HAague The Netherlands
REVIEW RETURNED	26-May-2014

GENERAL COMMENTS	Abstract 2/21 coclusions : last sentence If confirmed these results suggest etc Although there are many other reasons to avoid alcohol
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	<p>intake those data do not proof alcohol effects on future reproductive capacity since these data did not show any irreversible effect of alcohol intake nor any relation with the fertilizing potential of the studied individuals.</p> <p>Article summary Key message there is a reduced semen quality according to the semen parameters (WHO manual) but not according to proven fertilizing capacity of those samples. third bullet key message; Our findings are relevant etc There is only some evidence according to these data that there is a decline in a view standard semen parameters which are related to semen quality in a certain extent. However DE Jong, Rhemrev et al Andrologia 1-2013 showed that alcohol intake is not related to pregnancy outcome in a study comparing two groups subfertile and proven fertile group.</p> <p>Blz 4/21 last bullet Strange sentence The meaning ?? our study ?? etc</p> <p>Introduction 5/21 4th sentence ref3, latest studies did not confirm the positive effect of red wine (and scavengers) on survival and vascular disease in a large cohort study in Italy.</p> <p>In the discussion one should try to explain the increase of Free testosterone and its possible effect of fertility potential of the subsequent individual.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer Jaime Mendiola

This is a very interesting study that highlights the potential importance of alcohol consumption on male reproductive parameters. It is a cross-sectional study investigating the association between alcohol consumption and semen quality and reproductive hormone levels in young men. This is the first paper looking at the effects of recent vs. regular alcohol exposure on those reproductive parameters.

Thank you.

Specific Comments

Page 21/28. Table 1: It seems there are some missing data on lines 23-26, in 5th-95th columns.

The numbers in table 1 are missing due to few numbers instead 25 and 75 percentiles have been calculated. In suppl. Table binge and grouped binge percentages were not added, as these were 0 and 100, have been added.

There are more than a few results labelled by "data not shown", but might be of interest for the readers though. The authors could choose some of this information (the most relevant) and show it as supplementary tables as well.

We will be happy to add any results, generally we only showed results for last weeks intake and serum reproductive hormones and typical intake for semen quality as these were most significant which fitted the biological hypotheses.

Overall, The design and the methodologies are satisfactory, with a well round analysis. The discussion presented is appropriate and consistent. The consulted references are updated and

adequate. In my opinion, the paper presents novel data and is a well-organized manuscript that provides information that will be of interest to the readers of "BMJ Open".

Thank you.

Response to reviewer jpt Rhemrev

Abstract 2/21 conclusions : last sentence If confirmed these results suggest etc Although there are many other reasons to avoid alcohol intake those data do not proof alcohol effects on future reproductive capacity since these data did not show any irreversible effect of alcohol intake nor any relation with the fertilizing potential of the studied individuals.

The editor suggests the following conclusion: "These results suggest that young men should be advised to avoid habitual high alcohol intake, which may be beneficial both for general and reproductive health". We can of course change this but generally habitual alcohol intake is harmful to health.

Article summary Key message there is a reduced semen quality according to the semen parameters (WHO manual) but not according to proven fertilizing capacity of those samples.
third bullet key message; Our findings are relevant etc There is only some evidence according to these data that there is a decline in a few standard semen parameters which are related to semen quality to a certain extent. However DE Jong, Rhemrev et al Andrologia 1-2013 showed that alcohol intake is not related to pregnancy outcome in a study comparing two groups: subfertile and proven fertile group.

Key message has been changed: "Habitual alcohol intake was a stronger predictor for reduced semen quality (WHO manual), but not according to proven fertilizing capacity, already from a weekly intake above 5 units in a typical week, but was most pronounced for men with a typical intake of more than 25 units per week, than alcohol intake the week preceding the visit".

We find that it is not relevant to add references to other publications in the key message.

Blz 4/21

last bullet Strange sentence The meaning ?? our study ?? etc

Changed to: "Our study was large and consisted of young healthy men, of whom the majority had no knowledge of their fertility. It is therefore unlikely to have affected their motivation to participate."

Introduction 5/21 4th sentence ref3, latest studies did not confirm the positive effect of red wine (and scavengers) on survival and vascular disease in a large cohort study in Italy.

The following has been added: "Moderate alcohol consumption has been associated with reduced morbidity and mortality however not confirmed in all studies".

In the discussion one should try to explain the increase of Free testosterone and its possible effect of fertility potential of the subsequent individual.

We are not completely sure how to respond to this comment, we believe we have tried to suggest mechanisms for the increase in free testosterone, which we do not believe is beneficial for the fertility potential but due to decreased SHBG or decreased degradation

"If SHBG levels are affected this could explain the observed increase in cFT. Otherwise, it may be explained by alcohol detoxification leading to a changed metabolism of steroids in the liver. In

contrast, decreased testosterone levels have been reported in male alcoholics suggesting that habitual alcohol abuse may damage Leydig cells or impair the hypothalamic-pituitary-gonadal axis”.