Reviewer's report

Title: Vitamin C supplement use may protect against gallstones: an observational study on a randomly selected population

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Reviewer: Henning Wittenburg

Reviewer's report:

Major:
1. The authors describe the results of a cross-sectional study for gallstone prevalence rates in a small town in southern Germany. The study finds known risk factors that were associated with gallstone formation (age, female gender, age, BMI) and in addition identified alcohol consumption, physical activity and supplementation with vitamin C to protect from gallstone formation. The current paper focuses on the latter finding and the authors provide biological explanations from the literature in both animal models and in humans how vitamin C might protect from gallstones. The authors state that the identification of an influence of vitamin C on gallstone prevalence rates was the primary objective of the study. Was this pre-defined? The same population was employed earlier to study an influence of variation of the beta3 adrenergic receptor gene on gallstone formation (Klass et al., AJG 2007). This should be mentioned in the current manuscript.

2. The findings are interesting and well explained but one limitation certainly is the size of the study and the small number of participants that took vitamin C supplementation. This should be mentioned as a limitation of the study. In addition, the gallstone prevalence rate appears low compared to other studies. Do the authors agree and have an explanation for this finding?

2. Two very important risk factors for gallstone formation are rapid weight loss and the number of pregnancies. Was this assessed in the questionnaire used? Could these factors have influenced the results?

3. A positive family history was identified as an important risk factor for gallstones. The known genetic risk for gallstones should be discussed and the important results of the Swedish twin study could be referenced as a confirmation for genetic factors influencing gallstone risk (Katsika et al., Hepatology 2005).

4. Page 12: The sentence at the end of the first section of the discussion is unclear. Why did the results for the effect of lipid levels differ in the descriptive analysis and in the multiple regression models?

Minor:
1. In the abstract, the background section states the aims of the study. Instead, a sentence stating the background/hypothesis of the study could be given. The first sentence of the methods-section is lacking a verb.
2. Newer data on the economic impact of gallstones in the U.S. were published in GASTROENTEROLOGY earlier this year and should be cited in the first paragraph of the introduction.

3. In the introduction “liver cells” should be replaced by the more specific term “hepatocytes”.

4. In the introduction, the description of the results of the study by Gustafsson is unclear. The term “conditions of gallstone formation” should be replaced by a more detailed description of the results (changes in the bile salt composition and biliary phospholipids levels resulting in prolonged nucleation times).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.