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Lian-Sheng Ma
Editor-in-Chief

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Manuscript NO: 84988
Title: “Effect of lifestyle modification on hepatocellular carcinoma incidence and mortality among patients with chronic hepatitis B: A longitudinal nationwide population cohort study”

Dear Prof. Ma

We thank the editors and the reviewer for their interest in our paper and for their comments, which have helped us improve the manuscript substantially. We have revised the paper in response to these comments and we provide a point-by-point response to the concerns raised by the editors and the reviewer. All changes have been marked in the revised manuscript, and we also provide a clean copy of the paper. Please do not hesitate to contact us if you have any questions related to this paper.

Sincerely,

**Danbee Kang**, PhD, Professor, Department of Clinical Research Design and Evaluation, Sungkyunkwan University, Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea. Electronic address: dbee.kang@gmail.com., Seoul 06355, South Korea. dbee.kang@gmail.com

and

**Response to the Reviewer #1:**

**Specific Comments to Authors:**

**Summary Based on data from the Korean National Health Insurance Service between 2009, and 2017, 48,766 CHB with lifestyle modification (LSM) and 103,560 without LSM were collected by propensity matching. Their questionnaires at baseline and at follow-up period were analyzed for relationship to HCC development and mortality. They found that the adjusted HR for HCC and liver-related mortality was lower in the LSM group than the control group.**

**Comments:**

**1. The sentence in the result section of abstract "the adjusted hazard ratio (HR) for HCC and liver-related mortality was 0.92 [95% confidence interval (CI) 0.87–0.96] in the LSM group compared to 0.92 (95% CI 0.86–0.99) in the control group." is confusing. The risk of the control group should be 1.**

We are very sorry for the error in that sentence. In response to the reviewer's comment, we corrected the sentence as follows.

**Abstract (page 3, method section)**

*"With 48,766 patients in the LSM group and 103,560 in the control group, the adjusted hazard ratio (HR) for incident HCC and liver-related mortality was 0.92 [95% confidence interval (CI) 0.87–0.96] and 0.92 (95% CI 0.86–0.99) in the LSM group, respectively, compared with the control group."*

**2. Why would patients like to have lifestyle changes? The comorbidities in Table 1 were higher in the LSM group than the control group. Is it possible that patients changed their lifestyle due to the presence of some comorbidities?**

As the reviewer commented, people might abstain from drinking or smoking due to the presence of some comorbidities or deterioration of health status. However, unfortunately, our data do not have information on the reasons for changing health behavior. Therefore, we excluded participants who developed cancer or died within the first month of follow-up from baseline (health screening) to minimize potential reverse causality. With respect to the reviewer's comment, we discussed this as a limitation of the study.

**Discussion (paragraph 6)**

*"First, because this was a retrospective study, inevitable problems were encountered. Exclusion criteria were established to identify individuals who were expected to sustain their health status for an extended length of time at baseline. Nonetheless, the issue of reverse causation may remain. The K-NHIS does not provide information on the reasons for changing health behaviors. Consequently, sick quitter bias may arise in which people abstain from drinking or smoking because their health deteriorates to the point that they no longer find drinking or smoking enjoyable.[42] We further excluded participants who developed cancer or died within the first month of follow-up from baseline to minimize potential reverse causality."*

**3. Factors used in propensity matching is confusion. Please give a clear declaration.**

For propensity score (PS) matching, we conducted multivariable logistic regression to estimate the PS for the LSM group, using the following covariates: age, BMI, AST, ALT, GGT, presence of hypertension, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, whether the participant took antiviral medications at the current health screening visit, and drinking status (moderate or heavy), smoking status, daily alcohol consumption, and physical activity status (not at all or a little) at the previous health screening visit. Following the sequential target emulate trial methods, the covariates were updated over time. In response to the reviewer's comments, we have revised the sentence to improve clarity.

**Methods (paragraph 7)**

*"Furthermore, propensity score (PS) matching was performed to minimize the potential impact of confounders on outcomes. We conducted multivariable logistic regression using the following covariates: age, BMI, AST, ALT, GGT, presence of hypertension, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, whether the participant took antiviral medications at the current health screening visit, drinking status (moderate or heavy), smoking status, daily alcohol consumption, and physical activity status (not at all or a little) at the previous health screening visit to estimate the PS for the LSM group. Furthermore, if a patient had health screenings at different time points, we followed them from the date of their first screening, and then the time since the previous exam was included in the matching variables. Matching was performed using a greedy algorithm (caliper = 0.1). The control group was matched 2:1 with the LSM group in each trial. The covariate variables were updated at the start of each trial in the analysis. The covariates were updated over time following the sequential target emulate trial methods. This methodological strategy aligned the assessment of eligibility criteria, treatment assignment, and starting of follow-up, thus removing any immortal-time bias related to the delay between the health screening visit and adoption of healthy behaviors on clinical outcomes. We pooled data from all trials into a single*

*model and included the day of the trial's baseline in the analysis"*

**4. HCC, non-HCC cancer and mortality rates were used to evaluate the outcome between two groups. In prospective study, liver fibrosis and viral load were two major high risk factors that determine the outcome of chronic hepatitis B. Their relative risks of HCC and mortality are much higher than smoking or alcohol drinking. Unfortunately, these two factors were not included in this analysis.**

We absolutely agree with the reviewer that liver fibrosis and HBV viral load are two major risk factors for the outcome of chronic hepatitis B. Unfortunately, we were not able to include those variables as the data was not available. However, in Korea, antiviral agents are subject to a reimbursement policy based on the presence of liver cirrhosis, elevated AST or ALT levels, and HBV DNA levels. Therefore, we included the antiviral treatment as covariate. This would allow us to adjust for information on liver fibrosis and DNA levels. With respect to the reviewer's comment, we added the following discussion in the Discussion section.

**Discussion (paragraph 6)**

*"Fourth, we lacked several important variables for the outcome of CHB, for example, the degree of liver fibrosis and hepatitis B viral load. However, the administration of antiviral agents in Korea is subject to a reimbursement policy based on the presence of liver cirrhosis, elevated AST or ALT levels, and DNA levels. In this study, we attempted to partially account for liver fibrosis and DNA levels via adjusting for whether or not the patient received antiviral treatment."*

**5. The whole study was based on two questionnaires. True lifestyle modification may need a summary of multiple time points observations.**

We agree with the reviewer's comment that true lifestyle modification may need a summary of multiple time point's observations. Patients who assigned LSM groups could be changed during the study, which could potentially underestimate the LSM effects on incident cancer and mortality as our outcomes. Therefore, we took the sequential target trial emulation approach to account for such changes. This approach creates a sequence of "trials" from new time origins, and individuals are divided into those who have just initiated the LSM under investigation and those who have not yet initiated it. This method can help to reduce selection bias and provide more robust estimates of treatment effects. Therefore, we believe that our use of this approach, which is similar to an intention-to-treat analysis, provides a conservative

estimate of the association between LSM and outcomes. To account change from LSM to return to poor behavior, it might help to use per-protocol analysis. However, some patients did not participate in the next health screening visit, and it results another bias when we conducted per-protocol analysis. With respect to the reviewer's comment, we have updated the discussion as follows.

**Discussion (aragraph 6)**

*"Third, quantitative guidance for HCC risk and mortality reduction could not be offered because the dose- and time-effect linkages of LSM were not determined in this study. In addition, patients' assigned groups during the study might have changes, which could potentially underestimate the association between LSM and outcomes. However, additional biases in the analysis could have been introduced as some patients did not participate in the next health screening visit. Therefore, we performed target trial emulation to reduce selection bias and provide more robust estimates of treatment effects. Specifically, we were able to allocate the two groups at the "beginning" of induction, before subsequently emulating the randomization process using coarsened exact matching, through simultaneous determination of eligibility and assigning two arms."*

**6. Reference 2,4 did not focus on alcohol or smoking habits. The views of prospective cohort study concern about risk factors of HCC and mortality should be included.**

In response to the reviewer's comment, we updated references in the revision, including prospective cohort studies.

**Introduction (paragraph 2)**

*"Mounting evidence indicates that not only viral factors but also host factors, such as alcohol consumption, smoking, and obesity, and diet influence the prognosis of patients with CHB. (PMID 36114783, PMID 36130882, PMID 35973147, PMID 15601641)"*

**Response to the Reviewer #2:**

**Specific Comments to Authors:**

**In this manuscript, the authors described a trial emulation study to explore the relationship between a healthy lifestyle and disease progression in patients with hepatitis B had been investigated. It had been found that a healthy lifestyle can improve the disease outcome to some extent in patients with hepatitis B. I suggest accepting this manuscript**

**after they address the following concerns.**

**Specific comments:**

**1. The manuscript lacks specific details on healthy lifestyle practices, such as smoking cessation, alcohol cessation, and appropriate exercise, including specific questionnaire measurement. I would suggest that corresponding details should be provided for a better understanding of these practices.**

In response to the reviewer's comment, we have described detailed information regarding the questionnaire in Methods section.

**Methods section (paragraph 3)**

*"The main exposure was LSM including alcohol abstinence, smoking cessation, and regular exercise. The NHSE used standardized questionnaires to obtain information on alcohol drinking, smoking, and exercise. For the information on smoking status, participants were asked if they had ever smoked at least 100 cigarettes in their lifetime, based on the World Health Organization definition. Ever smokers were then asked regarding the duration of smoking and the mean number of cigarettes smoked per day. For drinking, participants were asked for the frequency (number of days per week) and quantity (amount of standard unit per occasion) of alcohol consumption. A standard unit was defined as a specialized cup for each type of alcohol such as beer, wine, Korean traditional alcohol (soju), or whisky. One standard unit contains roughly 8 g of ethanol in Korea, although different drinks can have very different alcohol content. The weekly amount of alcohol consumption was calculated by multiplying these two values. Alcohol intake was categorized into none, moderate (<40 g/day in women and <60 g/day in men), and heavy (≥40 g/day in women and ≥60 g/day in men). The exercise questionnaire used a 7-day recall method. The questionnaire was similar to the International Physical Activity Questionnaire (IPAQ)-Short form, which was modified by the Korean NHIS (see Supplement Figure 1). The questionnaire consisted of the following three questions: 1) How many days in the past week did you engage in vigorous activities that made you breathe much harder than normal for at least 20 min per day (e.g., running, aerobics, fast biking, climbing, etc.)?, 2) How many days in the past week did you engage in moderate activities that made you breathe somewhat harder than normal for at least 30 min per day (e.g., fast walking, doubles tennis, riding a bicycle at a normal speed, mopping, etc.)?, 3) How many days in the past week did you engage in light activities, such as walking for at least 30 min per day, adding up to a total of at least 30 min per day (e.g., walking to and from work or for leisure, light household chores, etc.)? This questionnaire has been widely used in previous studies. The main exposure was regular physical activity, which was defined as vigorous physical activity for ≥3 days per week (at least 60 min per week) or moderate physical activity for ≥5 days per week (at least 150 min per week)."*

**2. Providing information on changes in mortality rates over time to address deficiencies in the understanding of the relationship between patients' lifestyle changes and disease progression. Please provide information on changes in mortality rates over time.**

With respect to the reviewer's comments, we included information on changes in liver-related mortality rates over time in the Results section as follows. .

**Results (paragraph 3)**

*"During the follow-up period, 6,833 participants died, and 52.8% were liver-related death. The LSM group had a significantly lower risk of liver-related death compared with the control group over the entire period. The fully adjusted HR for all-cause mortality, when comparing the LSM group with the control group, was 0.94 (95% CI 0.90, 0.99) (Table 3). The fully adjusted HR for liver-related mortality, when comparing the LSM group with the control group, was 0.92 (95% CI 0.86, 0.99) (Table 3)."*

**3. Using the interval between questionnaires that investigates health behaviors as a measure of duration can to some extent quantitatively reflect the impact of LSM on HCC development.**

We emulated the sequential target trial from our cohort each time we compared the two arms of the trial. Patients were eligible for inclusion multiple times during follow-up if they were alive and had not exhibited at least one healthy behavior in previous time points (new-users design). At the baseline of each emulated trial, we classified patients as having exhibited healthy behavior if they had started at least one healthy behavior during their health screening visit, and potential confounding factors were measured. We defined day zero (the first follow-up) as the day of the health screening visit. If a patient had health screenings at different time points, we followed them from the date of their first screening and then the time since previous exam was included in the matching variables. This methodological strategy aligned the assessment of eligibility criteria, treatment assignment, and starting of follow-up, thus removing any immortal-time bias related to the delay between the health screening visit and the adoption of healthy behaviors on clinical outcomes. With respect to the reviewer's comments, we have included information in the Methods section to address the possibility of immortal time bias in our study design as follows:

**Methods (paragraph 7)**

*"Furthermore, propensity score (PS) matching was performed to minimize the potential impact of confounders on outcomes. We conducted multivariable logistic regression using the following covariates: age, BMI, AST, ALT, GGT, presence of hypertension, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, whether the participant took antiviral medications at the current health screening visit, drinking status (moderate or heavy), smoking status, daily alcohol consumption, and physical activity status (not at all or a little) at the previous health screening visit to estimate the PS for the LSM group. Furthermore, if a patient had health screenings at different time points, we followed them from the date of their first screening, and then the time since the previous exam was included in the matching variables. Matching was performed using a greedy algorithm (caliper = 0.1). The control group was matched 2:1 with the LSM group in each trial. The covariate variables were updated at the start of each trial in the analysis. The covariates were updated over time following the sequential target emulate trial methods. This methodological strategy aligned the assessment of eligibility criteria, treatment assignment, and starting of follow-up, thus removing any immortal-time bias related to the delay between the health screening visit and adoption of healthy behaviors on clinical outcomes. We pooled data from all trials into a single model and included the day of the trial's baseline in the analysis"*

**Response to the Reviewer #3:**

**Specific Comments to Authors:**

**The manuscript entitled "Effect of lifestyle modification on hepatocellular carcinoma incidence and mortality among patients with chronic hepatitis B: A longitudinal nationwide population cohort study" and authored by Park et al showed that unhealthy behaviors, including smoking, sedentary lifestyle, or alcohol drinking have adverse effect on the outcome among chronic hepatitis B (CHB) patients. Due to the limited data on the effect of healthier lifestyle modification (LSM), including quitting smoking, regular exercise, and quitting drinking, on the risk of hepatocellular carcinoma (HCC) in CHB patients, authors offer here this hypothetical randomized trial where they demonstrated that the LSM lowers the risk of developing HCC by using the nationwide database. The necessity for active counseling and therapeutic intervention for LSM in CHB patients was concluded. The following studies should be integrated to further support the discussion section: https://doi.org/10.4236/ajps.2018.96091, PMID: 32460808, PMID: 33255507.**

**Specific comments:**

**1. Proofreading would be useful.**

We have received English proofreading again and attached the English proofreading certificate together.

**2. In M &M, it is essential to verify if/how the patients' information used are anonymous.**

In this study, we used the K-NHIS data which all participants (patients) received an anonymous identification code to protect the patients' information and identity. In response to the reviewer's comment, we have added a sentence stating that the personal information has been anonymized.

**Methods (paragraph 1)**

*"All patients received an anonymous identification code in the K-NHIS data to protect the patients' information and identity."*

**3. References should be enriched with more diversified investigations that discuss in greater depth dietary effects. IF considered, results from the following studies could serve such a purpose: PMID: 35740022, PMID: 35517830, PMID: 35568708, PMID: 36432184.**

We agree with the reviewer's comment that dietary intake would influence the outcome of liver diseases. However, the K-NHIS does not contain dietary information, and we were not able to examine it. With respect to the reviewer's comment, we have briefly commented dietary effect on the outcome of CHB in the Introduction section in the revision as follows.

**Introduction (paragraph 2)**

*"Mounting evidence indicates that not only viral factors but also host factors, such as alcohol consumption, smoking, and obesity, and diet influence the prognosis of patients with CHB.[4-7]."*

**Introduction (paragraph 2)**

*"Evidence from observational studies and meta-analyses suggests that coffee consumption can reduce the incidence of HCC including in patients with CHB.(PMID 15868652, PMID 27111112) Furthermore, several studies have demonstrated that food-derived components*

*may have a positive impact on the progression of liver fibrosis (PMID 33255507, PMID 32460808) and the treatment of HCC.(PMID 36432184, PMID: 35740022, DOI 10.4236/ajps.2018.96091). "*

**Response to Company editor-in-chief**

**I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com**

In response to company editor-in-chief's comment, we revised the title as follows.

*"Effect of lifestyle modification on hepatocellular carcinoma incidence and mortality among patients with chronic hepatitis B"*

In addition, we have found that two of the references were cited incorrectly in the original manuscript and corrected the errors.

**Discussion (paragraph 2)**

*We included patients with CHB who drank, smoked, and did not exercise regularly. As the risk of developing HCC increases with the presence of more behavioral risk factors, (PMID 33187965) the participants of this study are expected to have the poorest prognosis.*

**Discussion (paragraph 3)**

*A meta-analysis on the effect of alcohol abstinence in patients with CHB predicted that limiting alcohol consumption would have a protective effect against the development of HCC even though quality research has not been conducted. (PMID: 21995442)*