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Dear Editor:

Thank you for arranging for peer-review of our manuscript 54031 which has helped us immensely to improve our manuscript. We would also like to thank the reviewers for taking the time to provide us with their kind feedback and constructive suggestions. We have revised the manuscript according to the comments and suggestions outlined below. We appreciate the opportunity to publish in your esteemed and well-respected journal, "World Journal of Hepatology." We hope the revised version meets your satisfaction and is acceptable for publication. Once again, thank you for giving us the opportunity to share our research findings with your audience.

Sincerely,

Sara Ghoneim

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Reviewer #1: Reviewer's code: 03262371
Dear editor Thanks for the invitation. My only question is regarding the case selection. Why did author only select patients with MI in 2018-2019, but NAFLD cases form 1999 to 2019? I think it can make an important bias.

Answer: Thank you for your kind review. We chose NASH/NAFLD cases since 1999-2019 and MI for the year of 2018-2019 for the following reasons: 1) In an attempt to establish a temporal relationship between NASH and MI. The risk must precede the event[1]. Therefore, NASH diagnosis must occur before the event of acute MI. Due to the inherent design of Explorys database, we included the diagnosis of NASH since 1999 and only included acute MI events within 2018-2019. This means that for any patient, the diagnosis of NASH could be coded anytime since 1999 prior to a coded diagnosis of MI in 2018-2019. It is possible that within 2018-2019, the diagnosis of MI was coded for a patient prior to the diagnosis of NASH, however, by selecting patients who have ever had a diagnosis of NASH since 1999 and only those with the diagnosis of acute MI within 2018-2019 we hope to **reduce the error rate and potential bias** that would significantly affect the validity of our study. Furthermore, this allowed us to establish an independent association between the diagnosis of NASH and acute MI events as reported by the multivariable regression analysis conducted in our study. We have revised the Patient selection section of the study to clarify this point. Finally, we apologize for the typographical error with MI. We only included acute MI within 2018-2019 but had used the term "acute MI" and "MI" interchangeably in the manuscript. We revised the Materials and Methods section to reflect this information.

Reference:

1. Hernán MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health. 2004;58:265-271. [PMID: 15026432 DOI:10.1136/jech.2002.006361].

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Reviewer # 2: Reviewer's code: 02445091

In this retrospective study among 43,170 NASH patients in US using a large national database, the authors concluded that (1) NASH conferred a higher risk of MI compared to patients without NASH; (2) NASH had a comparable association with MI as advanced age, male gender and diabetes mellitus; (3) in an overall unadjusted model, the prevalence of MI was significantly high in patients with NASH. The following are the points raised by this reviewer:

1. Major comments: Table 3 describes the absolute risk and relative risk of MI in patients with NASH compared to non-NASH. Did a gender base relative risk calculation possible among each age group?

   Answer: Thank you kindly for allowing us to improve our manuscript further. It was possible to calculate the relative risk of MI in patients with NASH based on gender in each age group. We have included Figure 2 to demonstrate our findings. The findings are very interesting and reflect the complex interplay of comorbidities, gender, inflammation/NASH on the overall risk of MI. Gender differences in the risk of MI were obvious. We elaborated on these findings in the discussion section. We hope the revised manuscript meets your satisfaction.

2. Minor comments: Many typographical errors found in the text that need to be corrected: 1. Core tip:…….severity might we? be able to... 2. Page 5: 'four fold increase in in? cardiovascular events

   Answer: Thank you for your constructive feedback. We have revised the manuscript accordingly.

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Reviewer #3: Reviewer's code: 03317140

The manuscript (54031) entitled " Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study" provided new information using the Explorys database, the author performed a national-based population study to investigate the association between NASH, a more severe subtype of NAFLD, and myocardial infarction in the United States. Unfortunately, this paper provided weak evidence to reveal a new finding from their database. Therefore, I think this paper needs a major revision to publish in the World Journal of Hepatology.

1. Baseline characteristics : First of all, Table 1 should show a difference between total cohort and NASH cohort. I could not make sure that the author excluded fatty liver disease, alcoholic hepatitis, and alcoholic fatty liver disease from total cohort. If they included in total cohort, it gave us analysis errors.

   Answer: Thank you for this observation. We have revised Table 1 to reflect the Baseline characteristics of the NASH cohort and overall study population. We included patients with only a diagnosis of "NASH" in the study and excluded patients with alcoholic hepatitis, alcoholic fatty liver disease and fatty liver disease.

2. NAFLD cohort : In principle, it is recommended to analyze the risks by NASH and NAFLD groups, because the effect of inflammation can be seen more clearly.

   Answer: Thank you for your feedback. Multiple studies have attempted to compare NASH and NAFLD groups and their associated cardiovascular risks but the results have been controversial[1-2]. As **NAFLD** is a spectrum disease that includes simple steatosis, NASH and eventually cirrhosis; it **may be prone to coding errors in Explorys**. Furthermore, due to the design of Explorys database, we are unable to explore direct temporal relationships and/or duration of disease. Additionally, Explorys offers population based data, not individual patient-level data. Therefore, it

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is not possible to use Explorys to accurately compare these two entities. Our study's aim was to evaluate whether the more metabolically aggressive form of NAFLD, which is NASH, was independently associated with acute cardiovascular events such as MI. The risk of cardiovascular disease is already established in patients with NAFLD[3-4]. But whether **NASH** is associated with increased risk of serious cardiovascular events is currently under investigation hence why treatments for NASH, but not NAFLD, are being investigated in clinical trials[5]. Our large cross-sectional study is unique in it looked exclusively at this subgroup of NAFLD and showed a significant relationship between NASH and the risk myocardial infarction.

References:

1. **Lazo M,** Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM. Non-alcoholic fatty liver disease and mortality among US adults; prospective cohort study. BMJ. 2011;343:d6891. [PMID: 22102439 DOI: 10.1136/bmj.d6891].
2. **Stepanova M**, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. Clin Gastroenterol Hepatol. 2012;10(6):646-650. [PMID: 22245962 DOI: 101016/j.cgh.2011.12.039].
3. **Ekstedt M**, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015; 61: 1547–1554. [PMID: 25125077 DOI: 10.1002/hep.27368].
4. **Söderberg C**, Stål P, Askling J, Glaumann H., Lindberg G., Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology. 2010; 51: 595–602. [PMID: 20014114 DOI: 10.1002/hep.23314].

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5. **Alkhouri N,** Lawitz E, Mazen Noureddin. Looking into the crystal ball: predicting the future challenges of fibrotic NASH treatment. *Hepatol Commun*. 2019;3(5):505-613. [PMID: 31061949 DOI: 10.1002/hep4.1342]

3. Classification of age : The number of patients by age is not clearly described, and this also describes baseline characteristics in other table or table 1, and subgroup analysis is needed to determine which factors closely affect MI development in each group. If the analysis by age group is not easy, it is necessary to see that the risk factors can be different for each age group by analyzing the data by cutting into 10-year-old units rather than analyzing them in 5-year-old units.

   Answer: Thank you for your observation. We revised Table 1 to include the number of patients by age. We created a subgroup analysis per your request looking specifically at age . Figure 1 and 2 provide subgroup analysis for each age group. In table 1, we choose specific comorbidities to include as they are in line with classical risk factors known to be associated with MI and NASH. We also adjusted for age in our multivariable model to assess whether there was an independent association between NASH and MI.

4. Definition of MI The distinction of MI is also ambiguous whether it is acute MI or old MI.

   Answer: Thank you for your feedback and we apologize for the typographical error, only patients with the diagnosis of "Acute MI" were included in this study. This increased the validity of our results and reduced coding errors as well as inherent biases with database study design.

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5. Whether DM, HTN, and dyslipidemia are all well controlled by drugs or not is an important part of MI development. The author should describe about that.

   Answer: Thank you kindly for your observation. As this is a cross sectional study using a large electronic medical record database, direct temporal relationships between risk factors such as DM, HTN, and dyslipidemia is not possible. The impact of interventions on these variables is also not possible by such databases. Explorys is a population-based platform and does not provide individual patient data.

   This database integrates patient information from over 50 states in the United States and includes over 60 million patient information. It has been validated in multiple fields including Hematology, Cardiology and Gastroenterology[1-3]. By utilizing this database, we were able to report an interesting finding that will need confirmation with prospective studies with long term follow up. We revised our discussion section in response to your comments. We hope you appreciate the revised manuscript.

References:

1. **Kaelber DC**, Foster W, Gilder J, Glider J, Love TE, Jain AK. Patient characteristics associated with venous thromboembolic events: a cohort study using pooled electronic health record data. *J Am Med Inform Assoc.* 2012; **19**: 965-972. [PMID: 22759621 DOI: 10.1136/amiajnl-2011-000782]
2. **El-Assaad I,** AL-Kindi SG, Saarel EV, Aziz PF. Lone pediatric atrial fibrillation in the united states: analysis of over 1500 cases. Pediatr Gardio. 2017;38:1004-1009. [PMID: 28374048 DOI: 10.1007/s00246-017-1608-7].
3. **Mansoor E,** Cooper GS. The 2010-2015 Prevalence of eosinophilic esophagitis in the USA: A population-based study. *Dig Dis Sci*. 2016;61(10):2928-2934. [PMID: 27250980 DOI: 10.1007/s10620-016-4204-4]

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6. Minor : Study design line 4, “from 1999 until 1999” is right?

Answer: We have corrected this error in the manuscript; thank you for pointing it out.

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Reviewer #4: Reviewer's code: 04025443

This is an interesting and a large-scale study of the myocardial infarction (MI) incidence and conditions that coincide these event. The manuscript is well-written, provides new scientific data on the factors associated with MI within a year (2018-2019) on a country-based level. The methods used by the authors are absolutely relevant to this certain aim, but seems to be not fully appropriate for the study purpose. This makes the scientific value of the study questionable. Below are the concerns about the study.

1. First – what was studied and in which groups? The aim of the study stated in the abstract and in the body of the manuscript differs. There is a discrepancy between time frame for identification of NAFLD/NASH patients and those with MI. Only cases of MI occurred within 1 year (2018-2019) where taken into the account while 20 years frame was taken for NAFLD. This does not allow to analyse neither risks nor incidence of MI in those with NAFLD and may be associated with an error related to random events. This approach can reveal the prevalence of NAFLD among the conditions found in patients with MI (if the study is focused on this condition) during a year (with a limitation of the coding, which, as it mentioned by the authors, could be not always correct).

   Answer: Thank you kindly for your constructive feedback. We have revised the abstract to be in line with what is discussed in the manuscript body. The purpose of our study was to evaluate the prevalence of MI in patients with NASH. Secondly, if there is an increased prevalence then it would be worthwhile knowing the temporal relationship between these 2 entities. Previous studies have demonstrated NAFLD to be an independent risk factor for cardiovascular disease and we hypothesized that this would be even more so true for NASH which represents a more active and aggressive spectrum of NAFLD. In order to establish NASH as a risk factor for MI

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one must demonstrate that the risk preceded the outcome[1]. Therefore, NASH diagnosis must occur before the event of MI. In order to do this in Explorys database, we included patients with diagnosis of NASH since 1999 and only included acute MI events within 2018-2019. This means that for any patient, the diagnosis of NASH could be coded anytime since 1999 prior to a coded diagnosis of MI in 2018-2019. It is possible that within 2018-2019, the diagnosis of MI was coded for a patient prior to the diagnosis of NASH, however, by selecting patients who have ever had a diagnosis of NASH since 1999 and only those with the diagnosis of acute MI within 2018-2019 we **reduced the error rate and potential bias** that would significantly affect the validity of our study. Furthermore, this allowed us to establish an independent association between the diagnosis of NASH and acute MI event as reported by the multivariable regression analysis the study. We have revised the Patient selection section of the study to clarify this point. This limitation is expected with any large scale population-based database utilized for observational studies. We also revised the body of manuscript to highlight the fact that our study reports the prevalence of MI in patients diagnosed with NASH. Because this is a cross-sectional study- also known as a prevalence study, we are able to calculate odds ratio, and relative risk of disease[2].

Reference:

1. Hernán MA. A definition of causal effect for epidemiological research. *J Epidemiol Community Health*. 2004;58:265-271. [PMID: 15026432 DOI:10.1136/jech.2002.006361].

2. There is another limitation which was not mentioned by the authors. NAFLD is a chronic condition and currently we don't have effective and specific treatment for it. However, some of the non-specific (and not highly specific) measures may be taken and are advised by EASL and AASLD. The authors searched for NAFLD codes in the

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database for the period of 20 years. But what was going on with the patient after diagnosis had been established? It seems hardly possible that a patient with the diagnosis of NAFLD confirmed, for example, in 1999 have been doing nothing for twenty years. At least part of the patients should have been made one or several attempts to lose weight, become more physically active. Some of them might have been taken measures to lower serum lipid concentrations, or affect insulin resistance, etc. The mentioned measures could make the risks of cardiovascular events lower.

Answer: Your observation is absolutely correct. Unfortunately, with retrospective population based-databases such as Explorys, its not possible to see which patient was able to lose weight, or was able to take measures to lower serum lipid concentrations etc. This database is a population-based software that provides population-level/cohort information and not individual case data. Furthermore, as this is observational study causality is hard to proof and large prospective clinical trials with long-term follow up are needed to elucidate the observations highlighted in your comments. Kindly note that we searched for and included only the diagnosis code for NASH.

3. On the Fig. 1, and in table 3 the "risks" of MI in NASH patients are shown. According to the Methods section, these "risks" correspond to 1 year only which should be discussed appropriately (and which is not really correct).

Answer: Thank you for your constructive feedback. We apologize if this was not clear from the manuscript but kindly note that the risk factors for MI we studied (traditional risk factors as well as NASH) were included since 1999 and were not just observed over 1 year. Only the diagnosis of "Acute MI" was limited to the 1 year (2018-2019) which was in the last year of the study. As this is a cross-sectional study, a type of observational study, to establish NASH as a possible risk for MI, any patient

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with the diagnosis of NASH since 1999 was selected so that this risk can precede the event of MI occurring in 2018-2019. We have revised the study design section of the study to further clarify this point.

4. The relative risk of IM in patients with NASH in the age group 40-44 y.o. is more than twice higher compared to those of 60-64 y.o. On the one hand it may reflect the need for prophylaxis of CVD, but on the other hand (considering time trend and the disease progression) may require double check for an unintentional mistake. Thus, in case of the importance of NASH in the structure of cardiovascular disease, and probable increase of its influence along the condition presence, it should have made the chances of MI in NASH patients higher in the older group. May I suggest to analyse association between MI and the duration of time after diagnosis of NAFLD/NASH was established?

   Answer: Thank you for your observation. We re-analysed the data and we confirm that this observation is not due to an unintentional mistake. Based on current US data, NASH is highly prevalent in patients within the age group of 40-49[1]. As NASH is an inflammatory disease one possible explanation for this observation is that the younger NASH population might have more inflammation and more aggressive disease than the older NASH group. Also, to calculate the relative risk, we evaluated the incidence risk in the exposed group/incidence risk in the nonexposed group. In the older population, it is possible that the non-NASH group (control) accumulated more traditional risk factors that may have reduced the relative contribution of inflammation on atherosclerosis; hence narrowing the differences between the 2 groups[2]. Lastly severity of NASH may not be attributed to age alone [3]. All of which would reduce the relative risk of MI in the older population from NASH as compared to their younger counterpart. We would suggest to view these results such

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that the risk NASH confers towards MI appears to be greatest in the younger population who possibly have a paucity of traditional cardiovascular risk factors. As patients age they may accumulate traditional cardiovascular risk factors (age itself being one) and hence the contribution of NASH towards the total burden of cardiovascular risk is reduced with age. That being said, its best practice to include absolute risk when reporting the relative risk, as the former provides insight into external validity of the study. The absolute risk of MI in the NASH and non-NASH groups increased with increasing age (Figure 1).

Reference:

1. **Sanyal AJ**. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology*. 2002; **123**(5) :1705-1725. [PMID: 12404245 DOI:10.1053/gast.2002.36572].
2. **Siegerink B**, Rohmann J. Impact of your results: Beyond the relative risk. *Res Pract Thromb Haemost*.2018;2(4):653-657. {DOI 10.1002/rht.12148].
3. **Noureddin M,** Yates KP, Vaughn IA, Neuschwander-Tetri BA, Sanyal AJ, McCullough A, Merriman R, Hameed B, Doo E, Kleiner DE, Behling C, Loomba R; NASH CRN. Clinical and histological determinants of nonalcoholic steatohepatitis and advanced fibrosis in elderly patients. *Hepatology*. 2013;58(5):1644-54. [PMID: 23686698 DOI: 10.1002/hep.26465].

5. May I suggest to analyse association between MI and the duration of time after diagnosis of NAFLD/NASH was established?

Answer: Thank you for your comment. The only way to establish this in population-based database such as Explorys was to select patients who had ever had a diagnosis of NASH prior to the diagnosis of MI. Hence we chose to allow a diagnosis of NASH since 1999 but limit the diagnosis of "Acute MI" to 2018-2019; thereby allowing for

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some establishment of temporal relationship. Direct temporal relationships are not possible with the Explorys database as it does not provide individual case level data. It is not possible to get information on how long after the diagnosis of NASH for each patient a diagnosis of MI was made. Longitudinal studies with serial liver biopsies will be required to investigate the progression of NAFLD and NASH to study their association with MI.

6. Please explain a note of "Informed consent was obtained from all participants" in Ethical Statements (page 17). If so, whether the ICF form was approved by an IRB/LEC?

   Answer: We apologize for this error. We revised this section and placed it on Page 1. As Explorys database provided de-identified population level information, it is exempt from IRB approval by our institution. A new informed consent document reflecting this information has also been uploaded into the system.

7. Please consider revision of the figure and tables titles. (For example Fig. 1 – Risks of MI in different age groups and according to the presence of NASH. Tab 1 – "demonstrates" is not appropriate. Table 2 – there is no "prevalence", but association of MI with certain conditions, Table 3 – please, explain the model "of what" is shown there.

   Answer: Thank you kindly for your constructive feedback. We have revised Figures and Table to reflect your comments.

8. I cannot agree with the conclusion that NASH increases the risk of MI in the American population. This statement requires temporal association which was not

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studied. According to the data described, in those with MI, NASH is a prevalent condition.

Answer: Thank you for your feedback. As this is a observational study/prevalence study, we have revised our manuscript to discuss NASH having a significant association with MI independent of traditional risk factors and that a diagnosis of MI is more prevalent in patients with NASH.

9. Sentences 2 and 3 in the Core tip are not relevant to the study.

Answer: We have revised the Core tip section accordingly. We hope the revised manuscript meets your satisfaction.

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Reviewer #5: Reviewer's code: 02861252

Very nice work The date should be corrected in the study design section only...

Answer: Thank you kindly for your generous feedback. The dates of the study design section have been corrected accordingly.

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Dear Editor Ying Duo:

Thank you for arranging for peer-review of our manuscript 54031 which has helped us immensely to improve our manuscript. We would also like to thank the reviewers for taking the time to provide us with their kind feedback and constructive suggestions. We have revised the manuscript according to the comments and suggestions outlined below. We appreciate the opportunity to publish in your esteemed and well-respected journal, "World Journal of Hepatology." We hope the revised version meets your satisfaction and is acceptable for publication. Once again, thank you for giving us the opportunity to share our research findings with your audience.

Sincerely,

Sara Ghoneim

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Reviewer's code: 04025443

Dear Editors!

Thank you for the opportunity to re-review the manuscript.

1. Unfortunately, I see no substantial changes in the manuscript.

Answer: Dear reviewer we have substantially revised the manuscript. Kindly see the following lines and pages to highlight all the changes we made as per your request.

Page 2: line 33-34. Page 3: line 55-56. Page 3: line 61-69. Page 5: line 113-114. Page 6: line 141-144. Page 7: line 162-165. Page 10: line 251-263. Page 11: 290-294.

2. The authors provided their answer, however they insist on the correctness of methods used in the study. I tried to make the error much visible by providing the diagram of what has happened below. According to the methods and the response to reviewers, the authors tried to evaluate the events of acute myocardial infarctions (MI) happened along the period of 2018-2019 years with special emphasis on the patients with the diagnosis of non-alcoholic steatohepatitis (NASH) established in 1999-2019 (fig. 1).

Fig 1. Study design

This approach makes possible to obtain the information about the prevalence of NASH among the patients with MI **in 2018-2019**, but NOT the chances of MI in NASH patients (fig. 2). The authors are not fully correct about the exposure and the event, as this statement imply a causal relationship. However, odds ratio does not, it is a measure of association between two events, especially in a retrospective studies.

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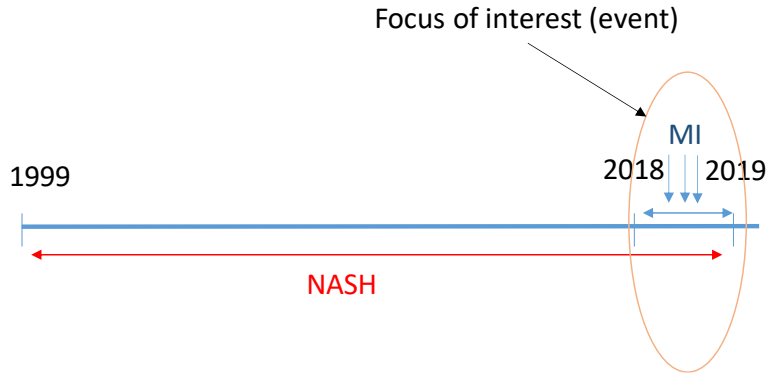

Fig. 2. What was studied

Answer: Dear reviewer: odds ratio looks at exposure and event in retrospective studies. **Therefore as you stated in your statement, our study is a retrospective study**, our hypothesis is that the exposure to NASH will result in the outcome of MI. This would be similar to if we studied the hypothesis of patients who smoked for 20 years and then developed MI (heart attack).

We looked at over 43000 patients who had been diagnosed with NASH since 1999, of those we wanted to see what was the chance they would have had MI in the last year of the study in 2018-2019. **Please see our diagrams** (Figure 1 & Figure 2) below to clarify the study methodology.

Hill's criteria requires 9 elements to be met for causality to be established. Therefore we are not establishing causality, we stated that our study is "an observational study and it precludes causality". **(please line 290-291, page 11).**

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Figure 1

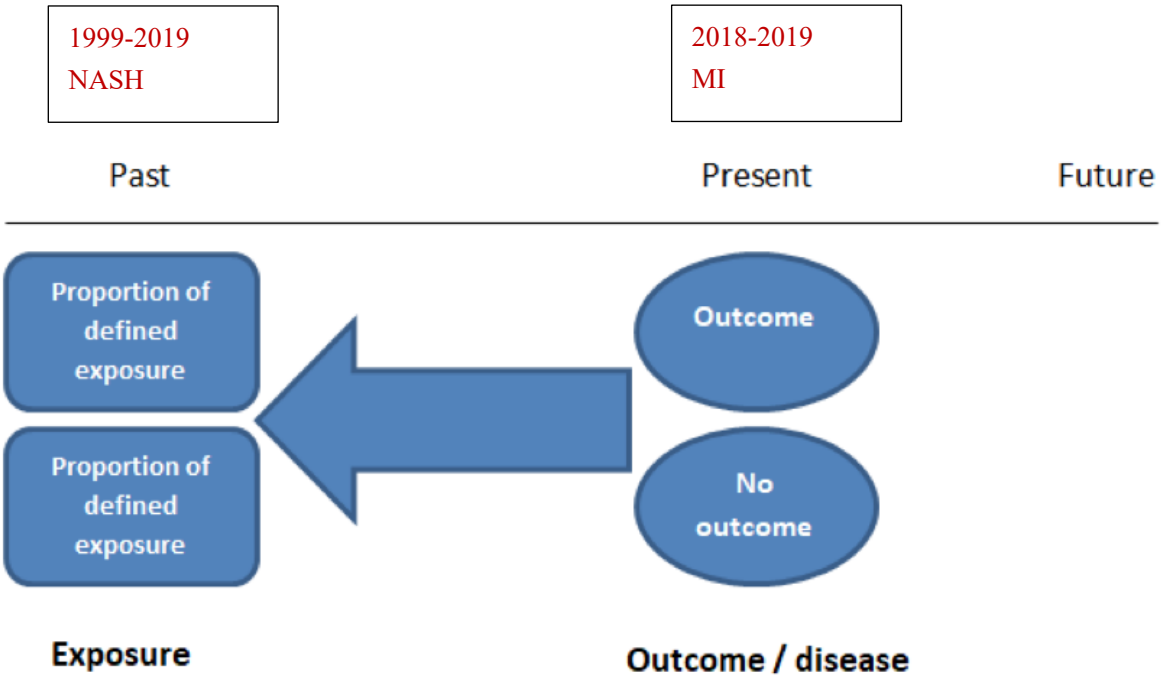

Figure 2:

Odds ratio

The odds ratio illustrates how strongly the presence or absence of a certain characteristic relates to the presence or absence of another characteristic. When applying it in public health, we can use the odds ratio to see if a certain outcome (e.g. developing ischemic heart disease) is associated with exposure to a hypothesized risk factor (e.g. smoking). With an odds ratio, *the outcome can be the starting point* with which we can determine the relative odds of someone having been exposed to a risk factor. Alternatively, we can also use it to describe the ratio of disease odds given the exposure status. Once we know the exposure and disease status of a research population, we can fill in their corresponding numbers in the following table.

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		Disease	
		+	-
Exposure	+	Diseased & exposed	Healthy & exposed
	-	Diseased & non-exposed	Healthy & non-exposed

To calculate the odds ratio, we use one of the following formulas (both give the same outcome):

$$\text{Odds ratio} = \frac{\text{Diseased \& exposed} \,/\, \text{Healthy \& exposed}}{\text{Diseased \& non-exposed} \,/\, \text{Healthy \& non-exposed}}$$

$$\text{Odds ratio} = \frac{\text{Diseased \& exposed} \,/\, \text{Diseased \& non-exposed}}{\text{Healthy \& exposed} \,/\, \text{Healthy \& non-exposed}}$$

References:

https://sciencebasedmedicine.org/causation-and-hills-criteria/

Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg*. 2010;126(6):2234-2242. doi:10.1097/PRS.0b013e3181f44abc

3. Narrowing the period for MI, and not taking into the account the possible events of MI happened on previous time interval (fig. 3) we may underestimate the prevalence of MI in those with NASH and put ourselves under the risk of bias associated with the random events.

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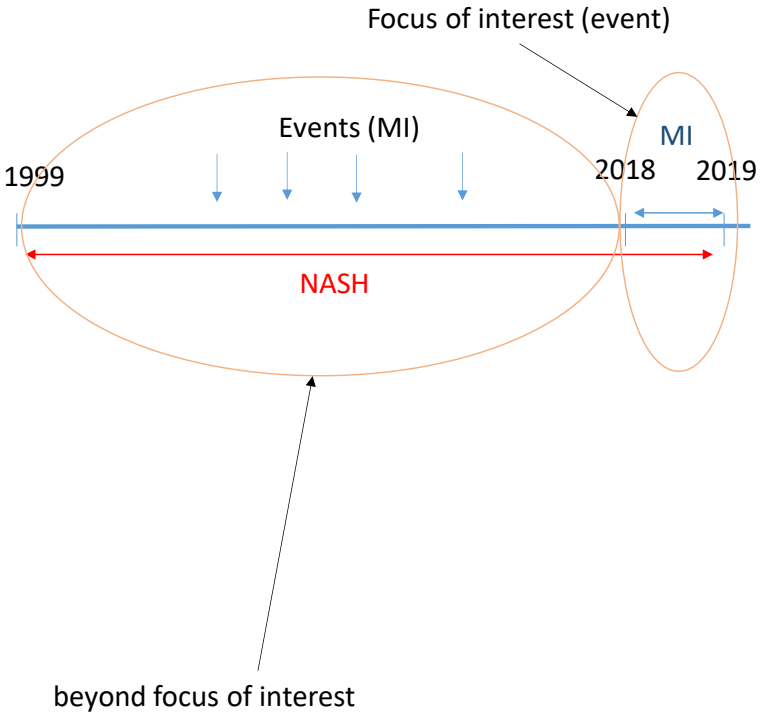

Fig. 3. The calculation of Odds ratio for MI in NASH should include all events of MI in patients with NASH.

Answer: We are not narrowing the event of MI. The exposure must occur before the outcome. Therefore, MI must occur after NASH, this reduces the error rate and coding bias if both diagnoses NASH and MI were present in the same time. NASH is a chronic disease while MI is an acute event. For example, if I smoked in 1999 my chance of MI (heart attack) in 1999 is less than if I smoked for 20 years and then got a heart attack in 2019. We are establishing a temporal relationship between the disease and outcome. Please see the below diagram to further clarify the methodology.

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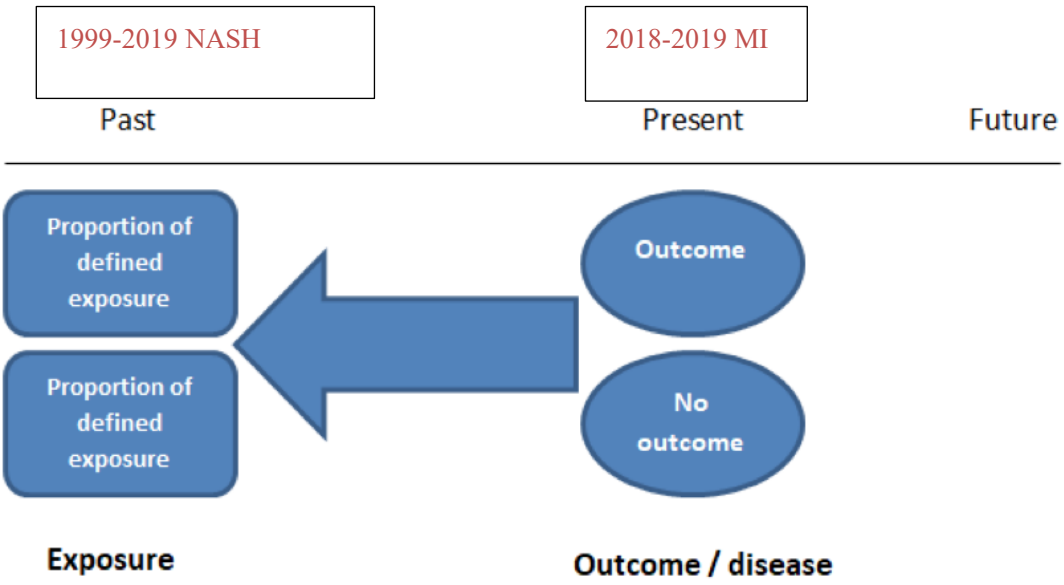

Random event bias or confounding was adjusted for in a multivariable logistic regression model please see (**page 6 for statistical analysis, line 159-162) .** We wanted to see the prevalence of an **acute event** such as MI in patients who had a chronic diagnosis of NASH. For example, patients with hypertension often have to have high blood pressure for many years before they have a heart attack. When utilizing a database, you must acknowledge coding errors, therefore we are establishing a timeline between NASH and the outcome of MI. Therefore, we are not under-reporting the prevalence and are actually reducing the coding error that might occur with databases. We provided you with the prevalence of MI in patients with NASH and without NASH. In NASH group, the prevalence of MI was 10.24% while in the non-NASH group it was 0.18%. (please see page 7, line 171-172, under Results). We are retrospectively studying the hypothesis of if patients have NASH, they will get the outcome which is MI.

4. According to the description of the odds ratio, odds ratio is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. Namely, all

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cases of MI should be calculated in patients with NASH for the same period. According to the manuscript, this is **not odds of MI in NASH (page 7, *Results*)**, but odds of NASH in MI

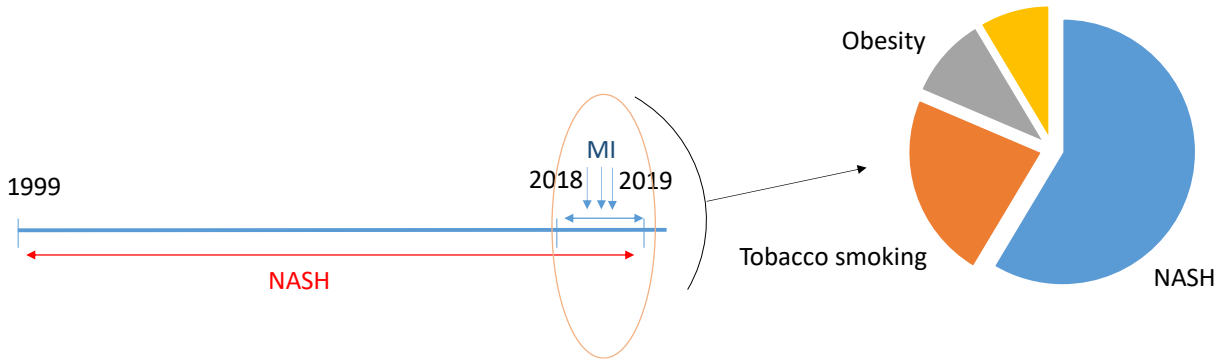

Fig 4. How odd are the odds.

Answer: Dear reviewer, the description of the odds ratio in retrospective studies is association between the exposure and outcome. As, this is a retrospective study, we defined NASH as the exposure and MI is the outcome. We studied the odds of MI in patients with NASH vs non-NASH. We even provided you with the % prevalence of MI in each group. I respectfully ask you to see the following lines 171-172 page 7. Please see below for our diagram to clarify the study methodology.

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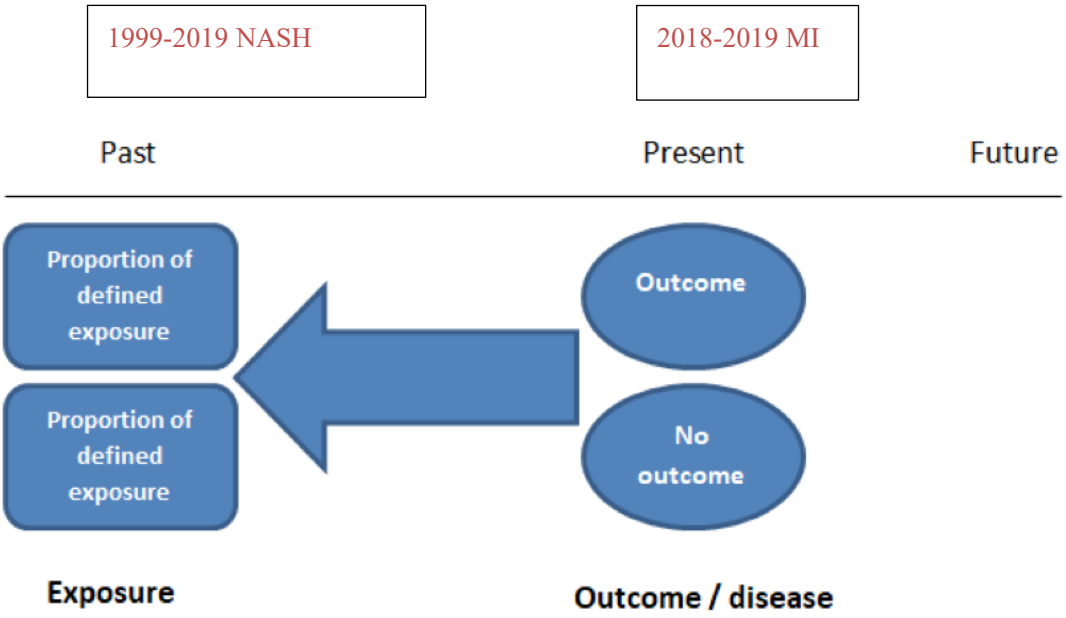

$$\text{Odds ratio} = \frac{\text{Diseased \& exposed / Healthy \& exposed}}{\text{Diseased \& non-exposed / Healthy \& non-exposed}}$$

$$\text{Odds ratio} = \frac{\text{Diseased \& exposed / Diseased \& non-exposed}}{\text{Healthy \& exposed / Healthy \& non-exposed}}$$

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5. Methods are described in somewhat weird way. For example, key point of statistical analysis comes as follows: "The prevalence of MI in each risk groups was calculated

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by dividing the number of patients with NASH in each risk group." (page 6, ***Statistical analysis***).

Answer: We have clarified this statement –Please see the new statement: The prevalence of MI was calculated by dividing the number of patients with MI in each risk group (NASH, hypertension, diabetes mellitus, obesity, hyperlipidemia, age, gender and smoking). Please see line 154-156 page 6.

6. Again, it seems that it was not possible to obtain correct data, as there is an uncertainty on the presence of NASH in 2019, in case the diagnosis has been established in 1999.

Answer: It is possible to obtain correct data because only patients who had NASH in 1999 are the same patients who would have had NASH in 2019. This was accounted for by only selecting those patients with active medical records. Please line 136 Patient selection subheading. This is why out of 55 million patients who are documented as **alive** in the database, only 43170 patients have ever been diagnosed with NASH since 1999-2019. NASH is a chronic diagnosis, and is the exposure. We then see who of the 43170 NASH patients developed MI in the last year of the study 2018-2019. Please see line 171-172 (page 7) of the study that says "The prevalence of MI in subjects with NASH was 10.24% and 0.18% in the non-NASH group. " **Please see (line 171-172 Page 7). We have given you a prevalence of 4420 patients with NASH that developed MI. (10.24%).**

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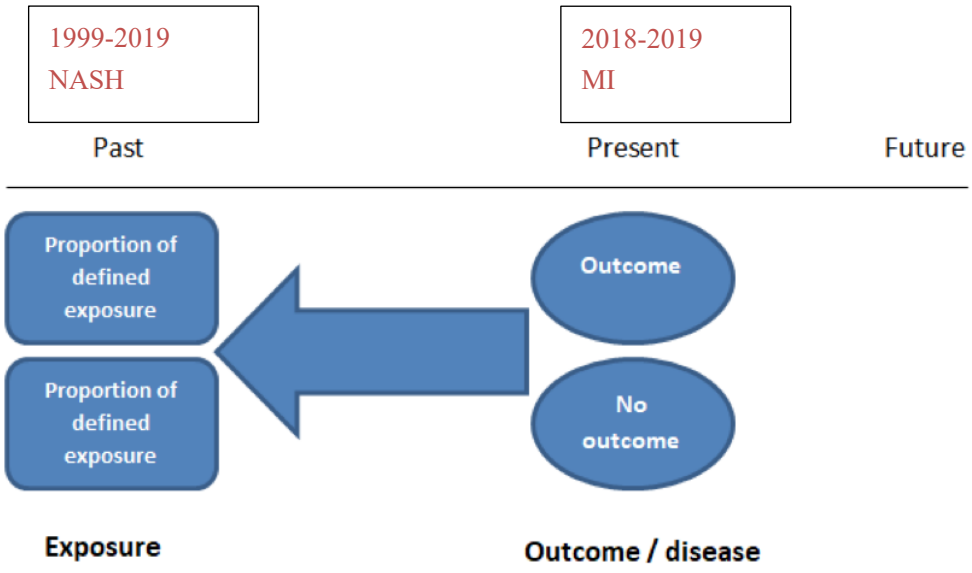

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7. Is it possible to perform an independent assessment of statistical correctness?

Answer: Dear reviewer. Yes it is possible to assess for statistical correctness. This is where multivariable logistic regression comes in to adjust for random error and confounding , as well as using the VIF to evaluate for collinearity. We have utilized this method to validate our data. Please see below for the new statement added to the manuscript to confirm the correctness of the statistical analysis. "**To adjust for possible confounding, a multivariable model adjusting for all covariates mentioned in univariate variables were added. Independence among covariate risk factors was assessed using the variance inflating factor (VIF) with cut-off of significant collinearity set at VIF > 1.5. "Goodness-of-fit" was assessed for all regression models using the Hosmer-Lemeshow test, with**

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P > 0.05 indicating good fit." **Please see page: 6-7.**

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Reviewer's code: 03317140

The manuscript (54031) was sufficiently revised according to the comments. However, please change the format of Tables 1 and 2 as shown in Table 3. Finally, I would like to suggest publishing this paper in the World Journal of Hepatology.

Answer: Thank your generous review. We have changed the format of Table 1 and 2 to resemble Table 3.

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TO AUTHORS

Reviewer's code: 02861252

Good work...

Answer: Thank you for your generous feedback.