June. 16th, 2023

Response to the Referees of "Impact of renaming NAFLD to MAFLD on disease prevalence, characteristics, and risk factors: a cross-sectional study"

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Impact of renaming NAFLD to MAFLD on disease prevalence, characteristics, and risk factors: a cross-sectional study" (Manuscript NO.: 85608). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: Ultrasound cannot detect mild, moderate, or severe hepatic steatosis.

Response: Thank you for your considerate questions. As reviewer suggested that ultrasound lacks sufficient sensitivity for lesser degrees of steatosis. There are several diagnostic tools for hepatic steatosis, but each has certain flaws as following:

a) The gold standard of hepatic steatosis is liver biopsy[1-2]. However, liver biopsy is invasive, the cost and incidence of adverse effects are high and few patients actually undergo this test in clinical practice, making it unsuited for epidemiological purposes[3].

b) Another measure of hepatic steatosis is the controlled attenuation parameter (CAP), CAP is a new ultrasound-based liver transient elastography ultrasound-based platform for the quantitative diagnosis of fatty liver. Typically measured in conjunction with VCTE, provides a point-of-care semiquantitative

assessment of hepatic steatosis, can detect more than 5% of hepatic steatosis and accurately identify lesser, mild and servious hepatic steatosis. However, CAP tends to overestimate the extent of hepatic steatosis when BMI > 30 kg/m2, the skin-to-peritoneal distance is >25 mm and the interquartile range (IQR) ⩾ 40 dB/m , the accuracy of CAP will descend[4-7], and need high dependence on operator experience, limited sampling range, large overlap in liver fibrosis staging data, inconsistent delineation of Cut off values and does not accurately monitor changes in liver fat[8].

c) The third methods is MRI – proton density fat fraction (PDFF), it is an accurate, reproducible, and precise MRI-based biomarker for liver fat quantification. This advantage is tempered by cost, patient acceptance[9], making it also unsuited for epidemiological purposes.

d) The clinical guideline point that ultrasound is the primary choice for MAFLD imaging evidence collection due to its high sensitivity, high specificity and relatively low cost[9]. The liver fatter diagnosis is based on features such as enhanced anterior field echogenicity of the liver ("bright liver"), distal field echogenicity and the lack of clarity of intrahepatic ductal structures. However, the sensitivity and specificity of B-mode ultrasound for the diagnosis of mild fatty liver is low and needs to be improved[4].

Before this retrospective study, we discussed our diagnostic criteria of MAFLD. Considering our data peculiarity that none participant has result of liver puncture and few results of VCTE, we had a group discussion and decided to choose the results of ultrasound to be the diagnostic criteria of hepatic steatosis. Thank you for your suggestions, we agree that ultrasound cannot detect mild, moderate, or severe hepatic steatosis. We have written the limitation of this study about the diagnostic criteria in the discussion. In the future, we will modify the diagnosis of hepatic steatosis in our next study.

2. **Response to comment:** In the opinion of some hepatologists, MAFLD and NAFLD are two different conditions. MAFLD may include viral hepatitis B or C.

NAFLD does not include viral hepatitis.

Response: We strongly agree with you. Although MAFLD was renamed from NAFLD, the scope of the two diseases is not completely identical, such as whether it includes viral hepatitis. This new term of MAFLD has its own disease epidemiology and clinical outcomes prompting efforts in studying its differences from NAFLD. This is also the purpose of this study.

3. **Response to comment**:The authors should distinguish between chronic renal failure and chronic renal disease.

Response: We are very sorry for our negligence of expression error. It should be "chronic renal disease", and we have corrected the original text and marked it in red.

4. **Response to comment**:The authors should analyze clearly how SUA, TBIL are related to chronic renal failure. Patients with chronic renal disease may have elevated SUA levels.

Response: Considering the Reviewer's suggestion, we have made additional clarifications. Please see line 236-240.

a) "Patients with chronic renal disease may have elevated SUA levels[11] and low level TBIL[12]".

5. **Response to comment:**The authors divided patients into groups: NAFLD, not NAFLD, MAFLD, not MAFLD. The authors should investigate one more group that includes both NAFLD and MAFLD.

Response: We have made correction according to the Reviewer' s comments. One

group that includes both NAFLD and MAFLD (MAFLD&NAFLD) was added in table1. Please see table 1.**Table 1. Clinical characteristics of the study participants MAFLD&NAFLD , with and without MAFLD and NAFLD**

Characteristics	All	MAFLD	Not MAFLD	NAFLD	Not NAFLD	MAFLD&NAFLD
N	85242	34485 (40.5%)	50757(59.5%)	26403 (31.0%)	58839(69.0%)	23905(28.0%)
Clinical characteristics						
Age, years		47.19±10.82	43.43±11.96	47.72±11.17	43.71±11.66	47.85±11.18
Sex, %						
male	49177	26627(77.21%)	22550(44.43%)	17927(67.90%)	31259(53.12%)	16350(68.40%)
female	36065	7858(22.79%)	28207(55.57%)	8476(32.10%)	27589(46.88%)	7555(31.60%)
BMI, kg/m2		26.79±2.69	22.44±2.48	26.29±2.84	23.29±3.12	26.64±2.71
Systolic blood pressure, mmHg		128.50±15.42	118.67±15.13	127.40±15.67	120.52±15.68	128.21±15.69
Diastolic blood pressure, mmHg		79.97±11.06	72.17±10.42	78.49±10.96	73.91±11.24	79.06±10.96
Waist circumference, cm		90.41±7.68	76.78±8.01	88.567±8.03	79.51±10.03	89.43±7.74
Hip circumference		97.81±5.52	91.53±5.03	96.92±5.63	92.80±5.83	97.42±5.55
Smoke, %						
Never	57452	19713(57.18%)	37739(74.36%)	17589(66.63%)	39863(67.76%)	15824(66.21%)
Always	20951	11443(33.19%)	9508(18.73%)	6663(25.24%)	14288(24.29%)	6127(25.64%)
Smoke in the past	3106	1666(4.83%)	1440(2.84%)	1047(3.97%)	2059(3.50%)	956 (4.00%)
Passive exposure to secondhand smoke	3720	1655(4.80%)	2065(4.07%)	1098(4.16%)	2622(4.46%)	992 (4.15%)
Drinks, %						
Yes	27567	14899(44.10%)	12668(25.31%)	5546(21.31%)	22021(38.09%)	5042(21.41%)
No	56275	18882(55.90%)	37393(74.69%)	20478(78.69%)	35797(61.91%)	18506(78.59%)
Type 2 diabetes mellitus, %						
Yes	2596	1775(5.15%)	821(1.62%)	1287(5.12%)	1309(2.22%)	1287 (5.38%)

No	82645	32710(94.85%)	49935(98.38%)	25116(94.88%)	57529(97.78%)	22618(94.61%)
Inappetence						
Never	57298	24017(69.66%)	33281(65.57%)	18671(70.73%)	38627(65.65%)	16988(71.08%)
Occasionally	24989	9446(27.40%)	15543(30.62%)	6976(26.43%)	18013(30.62%)	6232(26.08%)
Often	2947	1016(2.95%)	1931(3.80%)	751(2.84%)	2196(3.73%)	680(2.85%)
Take the initiative to acquire medical knowledge, %						
Yes	48284	19268(55.88%)	29016(57.17%)	14989(56.78%)	33295(56.59%)	13534(56.63%)
No	36946	15210(44.12%)	21736(42.83%)	11409(43.22%)	25537(43.41%)	10366(43.37%)
Laboratory inspection						
Triglycerides, mg/dL		2.67±2.40	1.32±1.00	2.38±2.07	1.63±1.67	2.47±2.14
Total cholesterol, mg/dL		5.24±1.04	4.89±0.92	5.19±1.00	4.96±0.97	5.19±1.01
LDL-Cholesterol, mg/dL		2.88±0.89	2.86±0.78	2.94±0.87	2.84±0.80	2.92±0.88
HDL-Cholesterol, mg/dL		1.18±0.24	1.42±0.30	1.19±0.24	1.38±0.31	1.18±0.23
TBIL (μmol/L)		13.38±5.15	13.52±5.28	13.24±5.15	13.56±5.26	13.21±5.16
AST, IU/L		26.83±18.10	22.55±17.75	25.76±13.67	23.74±19.70	26.00±14.07
ALT, IU/L		35.73±27.93	21.28±21.60	33.86±25.81	24.09±24.57	34.59±26.44
A/G		1.76±0.29	1.76±0.31	1.75±0.28	1.77±0.31	1.74±0.28
Fasting plasma glucose, mg/dL		5.96±1.68	5.32±1.77	5.88±1.62	5.44±1.81	5.93±1.65
Glycated hemoglobin		5.91±0.96	5.52±0.63	5.90±0.95	5.59±0.72	5.92±0.95
Urea nitrogen		4.97±1.23	4.71±1.31	4.95±1.23	4.75±1.31	4.97±1.23
Uric acid, mg/dL		385.23±85.79	312.61±79.14	372.25±85.03	328.43±87.85	375.02±85.10
Platelets ($\times 10^9$/L)		227.84±54.33	225.02±55.02	229.55±54.92	224.64±54.61	229.55±55.11
Total bile acid		4.36±5.89	3.96±5.25	4.24±5.13	4.07±5.71	4.29±5.25
Creatinine (μmol/L)		77.32±16.64	78.80±394.01	75.62±17.34	79.36±365.95	75.84±17.52
≥2 metabolic abnormalities, n %）						
Yes	38399	27536(79.85%)	10863(21.40%)	19018(72.03%)	19381(32.94%)	19018 (79.56%)

No	46843	6949(20.15%)	39894(78.60%)	7385(27.97%)	39458(67.06%)	4887(20.44%)
Lifestyle management						
Do you often eat late night snacks						
Never	56798	23097(66.99%)	33701(66.40%)	19221(72.81%)	37577(63.87%)	17377(72.70%)
Occasionally	25624	10204(29.59%)	15420(30.38%)	6579(24.92%)	19045(32.37%)	5971(24.98%)
Often	2811	1179(3.42%)	1632(3.22%)	600(2.27%)	2211(3.76%)	554(2.32%)
Crapulent						
Yes	5750	3175(9.21%)	2575(5.07%)	1799(6.81%)	3951(6.72%)	1706 (7.14%)
No	79484	31305(90.79%)	48179(94.93%)	24600(93.19%)	54884(93.28%)	22195(92.86%)
Food preference						
Light	35389	12278(35.61%)	23111(45.54%)	10875(41.20%)	24514(41.67%)	9665(40.44%)
Briny	26194	12755(36.99%)	13439(26.48%)	8694(32.93%)	17500(29.74%)	8014(33.53%)
Unclear	23649	9446(27.40%)	14203(27.98%)	6829(25.87%)	16820(28.59%)	6221(26.03%)
Drink beverage						
Never	46065	18399(82.24%)	27666(82.51%)	13920(81.90%)	32145(82.27%)	12602(81.58%)
Occasionally	9198	3653(16.33%)	5545(16.54%)	2830(16.65%)	6368(16.30%)	2624 (16.99%)
Often	806	320(1.43%)	320(0.95%)	246(1.45%)	560(1.43%)	222 (1.44%)
Exercise frequency						
1-2times/week	21380	8441(39.52%)	12939(41.37%)	6477(39.69%)	14903(41.04%)	5820(39.48%)
3-5times/week	21162	8672(40.60%)	12490(39.94%)	6503(39.85%)	14659(40.36%)	5887(39.93%)
＞5times/week	10093	4247(19.88%)	5846(18.69%)	3338(20.46%)	6755(18.60%)	3036 (20.59%)
Exercise training						
Yes	52829	21444(62.20%)	31385(61.84%)	16404(62.15%)	36425(61.91%)	14825(62.03%)
No	32400	13033(37.80%)	19367(38.16%)	9991(37.85%)	22409(38.09%)	9073(37.97%)
Exercise duration						
<30min	12701	4950(23.17%)	7751(24.78%)	4085(25.03%)	8616(23.72%)	3662(24.84%)
30-60min	30669	12575(58.87%)	18094(57.85%)	9475(58.06%)	21194(58.36%)	8568(58.12%)
>60min	9266	3836(17.96%)	5430(17.36%)	2758(16.90%)	6508(17.92%)	2513 (17.05%)
Labour intensity						
Light physical labor	77907	31651(91.78%)	46256(91.13%)	24186(91.60%)	53721(91.30%)	21844(91.38%)

Moderate physical labor	6282	2463(7.14%)	3819(7.52%)	1940(7.35%)	4342(7.38%)	1808 (7.56%)
Heavy physical labor	1053	371(1.08%)	682(1.34%)	277(1.05%)	776(1.32%)	253(1.06%)
Psychological states						
Irritability						
Never	43964	18836(54.63%)	25128(49.51%)	14745(55.85%)	29219(49.67%)	13428(56.18%)
Occasionally	35294	13631(39.53%)	21663(42.68%)	10152(38.46%)	25142(42.74%)	9103(38.09%)
Often	5973	2012(5.84%)	3961(7.80%)	1502(5.69%)	4471(7.60%)	1370 (5.73%)
Tense and unrelaxed						
Never	54907	22753(65.99%)	31154(61.38%)	17813(67.47%)	36094(61.35%)	16156(67.59%)
Occasionally	26438	10081(29.24%)	16357(32.23%)	7379(27.95%)	19059(32.39%)	6638(27.77%)
Often	4890	1647(4.78%)	3243(6.39%)	1208(4.58%)	3682(6.26%)	1108 (4.64%)
Anxious						
Never	55837	23594(68.43%)	32243(63.53%)	18363(69.56%)	37474(63.69%)	16670(69.75%)
Occasionally	25399	9578(27.78%)	15821(31.17%)	7059(26.74%)	18340(31.17%)	6337(26.51%)
Often	3999	1307(3.79%)	2692(5.30%)	977(3.70%)	3022(5.14%)	894 (3.74%)
Depress						
Never	59871	25192(73.06%)	34679(68.32%)	19610(74.28%)	40261(68.43%)	17811(74.52%)
Occasionally	22155	8306(24.09%)	13849(27.29%)	6040(22.88%)	16115(27.39%)	5410(22.63%)
Often	3210	982(2.85%)	2228(4.39%)	750(2.84%)	2460(4.18%)	681 (2.85%)
Sleep						
Well	33017	14188(41.15%)	18829(37.10%)	11027(41.77%)	21990(37.38%)	10043(42.02%)
Moderate	43242	16974(49.23%)	26268(51.76%)	12894(48.84%)	30348(51.58%)	11627(48.65%)
Bad	8974	3318(9.62%)	5656(11.14%)	2478(9.39%)	6496(11.04%)	2231 (9.33%)

6. **Response to comment:** In Tables 1 and 2, there were many variables. However, in the discussion, the authors did not mention them.

Response: Reviewing the tables, we found that the results of the t-test and chi-square in the original Table 1 and the univariate analysis in Table 2 may be duplicated. Therefore, we removed the p-values from Table 1 and added a column for the both MAFLD and NAFLD disease (MAFLD&NAFLD), as the reviewer's comment in item

5. The clinical characteristics of the disease can be seen in Table 1. Previously we had to cut some of the discussion due to the journal's word limit, but now, based on the reviewers' comments, we have tried to add as much as possible, and all variables of significance in the multi-factor regression are fully discussed, as detailed in line 292-323.

Special thanks to you for your good comments.

Reviewer #2:

1. **Response to comment**:The authors should incorporate a discussion on the differences and advantages of using VCTE for diagnosing NAFLD or MAFLD. This is important because VCTE has been shown to provide more accurate diagnosis compared to other diagnostic methods, due to its ability to detect liver stiffness, a key feature of these conditions. Relevant studies to be cited in this regard could include: doi: 10.1016/j.numecd.2023.03.005); doi: 10.3389/fendo.2023.1160625; doi: 10.3389/fimmu.2022.925690); doi: 10.3389/fendo.2022.857110.

Response: Considering the Reviewer’s suggestion, we have read these references carefully[13-17] as an important paper reference and added on the differences and advantages of using VCTE for diagnosing NAFLD or MAFLD on discussion. The modifications have been highlighted in red in the original text. Please see lines 343-348.

2. **Response to comment:** while this study has several strengths, particularly in its large sample size and detailed analysis, some areas could be improved, particularly in the discussion of diagnostic methods.

Response: As Reviewer suggested that this is one of our shortcomings. According to the suggestions of reviewer, we have provided more details in the discussion of diagnostic methods. And we have stated the limitations in discussion. The result can be used as a preliminary reference and look forward to in-depth discussions based on a more accurate diagnosis in the future. Please see lines 343-348.

Special thanks to you for your good comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And we marked the changes in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

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