Author’s response to reviews

Title: Impact of metabolically healthy obesity on the risk of incident gastric cancer: a population-based cohort study

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Author’s response to reviews:

Dear Ms. Zahra Bahadoran

Thank you for your kind letter concerning our manuscript on Oct 26, 2019.

Enclosed please find our revised manuscript newly entitled “Impact of metabolically healthy obesity on the risk of incident gastric cancer: a population-based cohort study”, manuscript ID of which is BEND-D-19-00247.

At first, we would like to thank reviewers for constructive comments on our manuscript.

According to the reviewers’ comments, we have carefully revised our manuscript.

Responses to reviewers’ comments are described as below.

All authors have agreed to authorship and order of authorship for this revised manuscript and that all authors have the appropriate permissions and rights to the reported data.

Your kind consideration of this paper would be greatly appreciated.
Yours faithfully,

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Response to Reviewer 1

1. Potential conflict of interest: this is an area of concern and any commercial bias needs to be eliminated.

Response

Thank you for your comment. As you say, any commercial bias needs to be eliminated.

In the Competing interest section, we only showed the potential conflict of interest. These financial supports from commercial sponsors were outside the submitted work. Thus, these commercial sponsors were not involved in this study.

2. Abstract: How does this conclusion impact management of gastric cancer. Please explain the utility of your study.

Response

Thank you for your valuable comment. We revealed that individuals with MAO, but not those with MHO, had an elevated risk for incident gastric cancer. Thus, we should focus more on the presence of metabolic abnormalities rather than obesity itself for incident gastric cancer. According to your comment, we have added this point in the conclusion of the Abstract section (Page 3 Line 62,63) described as below.

“Conclusions: This study shows that individuals with MAO, but not those with MHO, had an elevated risk for incident gastric cancer. Thus, we should focus more on the presence of metabolic abnormalities rather than obesity itself for incident gastric cancer.”

Response to Reviewer 2

1- In the abstract section, background needs to be revised to be more concise and focused on the main hypothesis of the study.
Response

Thank you for your suggestion. According to your suggestion, we have revised the background in the Abstract section (Page 3, Line 43-45) described as below.

“Background: The risk of colon or breast cancer in metabolically healthy obese (MHO) were lower than that in metabolically abnormal obese (MAO). We hypothesized that the risk of incident gastric cancer in MHO is lower than that in MAO.”

2- For follow-up period in the abstract, please provide median and inter-quartile range rather than mean.

Response

Thank you for your comment. According to your comment, we have provided median and inter-quartile range in the Abstract section (Page 3, Line 55,56) described as below.

“Over the median follow-up period of 5.5 (2.9-9.4) years, incident rate of gastric cancer was 0.65 per 1000 persons-years.”

3- Please provide incidence of gastric cancer as case per 1000 person-year.

Response

Thank you for your comment. According to your comment, we have provided incidence of gastric cancer as case per 1000 person-year in the Abstract (Page 3, Line 55,56) and Results (Page 10, Line 203-205) sections and Table 2.

“Over the median follow-up period of 5.5 (2.9-9.4) years, incident rate of gastric cancer was 0.65 per 1000 persons-years. Incident rate of MHNO, MHO, MANO and MAO were 0.33, 0.25, 0.80 and 1.21 per 1000 persons-years, respectively.”

4- Please provide a brief background about gastric cancer and obesity among Japanese population, where the study was conducted. Such information can highlight the importance of the study in this population.

Response

Thank you for your comment. The association between gastric cancer and obesity among Japanese population is controversial. Thus, we have mentioned this point in the Background (Page 5, Line 99,100) section described as below.

“The association between gastric cancer and obesity among Japanese population is controversial [14,15].”


5- The authors need to provide a focused background about difference between metabolically healthy or metabolically abnormal obese subjects; why the authors hypothesized that these two clinical status may be different for development of cancer? This question needs to be underlined and well clarified in the introduction section. This would help readers to judge the analytical logic and overall credibility of the study.

Response

Thank you for your valuable suggestion. As you say, this point is important for this study. Previous studies have shown that not only the risk of T2DM, CKD and CVD, but also the risk of colon cancer and breast cancer is lower in metabolically healthy obesity than in metabolically abnormal obese individuals. Previous meta-analyses showed that obesity was a risk factor for incident gastric cancer. On the other hand, the association between gastric cancer and obesity among Japanese population is controversial. These studies did not consider the presence of metabolic abnormalities. Thus, we thought that metabolic abnormalities might be involved in lack of consistent association between gastric cancer and obesity. According to your suggestion, we have added these points in the Background (Page 5, Line 99-104) section described as below.

“The association between gastric cancer and obesity among Japanese population is controversial [14,15]. These studies did not consider the presence of metabolic abnormalities. In contrast, there is an association between metabolic syndrome and incidence of gastric cancer [16-19]. Thus, we thought that not obesity itself, but the presence of metabolic abnormalities, which often accompany with obesity, have an important meaning for gastric cancer.”


Response

Thank you for your valuable suggestion. According to your suggestion, we have added association between metabolic syndrome and incidence of gastric cancer in the Background (Page 5, Line 99-104) and Discussion (Page 10,11, Line 226-230) sections described as below.

“The association between gastric cancer and obesity among Japanese population is controversial [14,15]. These studies did not consider the presence of metabolic abnormalities. In contrast, there is an association between metabolic syndrome and incidence of gastric cancer [16-19]. Thus, we thought that not obesity itself, but the presence of metabolic abnormalities, which often accompany with obesity, have an important meaning for gastric cancer.”

“In fact, previous studies revealed the association between metabolic syndrome and incidence of gastric cancer [16-19].“

“As to why MAO, but not MHO, was associated with a higher risk of incident gastric cancer, there were several possible explanations. It has been reported that metabolic syndrome is associated with gastric cancer [16-19,32].”

In the method section, study sampling needs more details; sampling method and study population selection for the cohort should be described in brief. The authors also need to describe how their study population is representative for target population and how their study findings can be extrapolated to Japanese population? In specifying this information, readers are apprised precisely about what sampling method was used and its possible adequacy or inadequacy for supporting the conclusion.

Response

Thank you for your valuable comment. As you say, to show more details of sampling and the target population is important for extrapolation of this results. According to your comment, we have added this point in the Study population section (Page 6, Line 115-118) described as below.

“The purpose of medical health-checkup was to promote public health by early detection of chronic diseases and their risk factors and about 60-70% examiners received the examinations, repeatedly; thus, the participants represent apparently healthy individuals. Most of the participants of this medical health-checkup were employees of various companies and local governmental organizations in Gifu, Japan, and their consorts.”
8- In the statistical section the authors should perfume further analysis to indicate how each metabolic abnormality (hypertension, impaired fasting glucose, hypertriglyceridemia and low high density lipoprotein-cholesterol) had contributed in development of gastric cancer. By such analysis they can discuss which abnormality has greater potential impact in predicting gastric cancer.

Response

Thank you for your valuable suggestion. According to your suggestion, we have perfumed further analysis to indicate how each metabolic abnormality had contributed in development of gastric cancer. Crude hazard ratio of presence of impaired fasting plasma glucose and/or diabetes, hypertension, elevated triglycerides and low HDL-cholesterol were 2.67 ([1.71-4.17], p <0.001), 2.28 ([1.44-3.56], p <0.001), 1.69 ([0.94-2.85], p = 0.077) and 1.41 ([0.85-2.26], p = 0.180), respectively. We have added these results in Table 3 and the Statistical analysis (Page 9, Line 189-191) and Results sections (Page 10, Line 211-213) described as below.

“Furthermore, we used the Cox Proportional Hazards Model to calculate the HR of each metabolic abnormality (hypertension, impaired fasting glucose, hypertriglyceridemia and low HDL-cholesterol).”

“Furthermore, presence of impaired fasting plasma glucose and/or diabetes, and hypertension were associated with incident gastric cancer (Table 3).”

In addition, we have also revised the Discussion section (Page 11, Line 228-246) described as below.

“As to why MAO, but not MHO, was associated with a higher risk of incident gastric cancer, there were several possible explanations. It has been reported that metabolic syndrome is associated with gastric cancer [16-19,32]. In this study, we showed that the presence of metabolic abnormalities, especially impaired fasting plasma glucose and/or diabetes and hypertension, were associated with gastric cancer, which was almost the same as previous studies [33,34]. Inflammation, as represented by elevation of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), is known to be closely associated with not only obesity [35], but also the metabolic abnormalities, including impaired fasting plasma glucose and hypertension [36]. Inflammation leads to the development of gastric cancer by stimulating proliferation and inhibiting apoptosis of human gastric cancer cells [37]. Formation of reactive oxygen species (ROS) by advanced glycation end products [38] leads to DNA damage and development of gastric cancer. In addition, tumor cell progression is stimulated by enhancing the mTOR signaling pathways through an increase in insulin-like growth factor 1 (IGF-1) [39]. On the other hand, it has been reported that the levels of inflammation and IGF-1 in MHO were lower than those in MAO [40,41]. Collectively, these results could explain why the MAO phenotype, but not the MHO phenotype, was associated with a higher risk of incident gastric cancer.”

9- Please indicate how confounding variables were selected for the statistical models and how the Cox Proportional Hazard Models were fit for covariates. The authors need to
check P for Entry (PE) for each potential confounder by univariate model. Please also provide HR (95% CI) and P value for potential confounders, both in univariate and multivariate models.

Response

Thank you for your comment. In this study, we selected factors reported as risks in previous studies as confounding variables. Thus, we have added the references of the risks in Statistical analysis (Page 9, Line 184-186) section described as below. In addition, we have also checked the HR (95% CI) and p value for potential confounders in Supplemental Table 1.

“We considered five potential confounders as covariates: age, sex, alcohol consumption [28], pack-years [29], and exercise [30].”


10- In the result section, the authors should provide demographic background of the whole study population (e.g. mean ± SD of age, sex distribution, mean ± SD of BMI, waist circumference, etc.) rather than those provided in Table 1 for the groups.

Response

Thank you for your suggestion. According to your suggestion, we have provided the demographic background of the whole study population in the Results section (Page 9, Line 199-200) described as below.

“The baseline characteristics of the participants are shown in Table 1. Average age and BMI of this study participants were 45.5 ± 9.5 years old and 22.6 ± 3.3 kg/m2 and 59.9% (11,782) were men. In addition, both BMI and metabolic parameters, including blood pressure, fasting plasma glucose, triglycerides and HDL cholesterol, were different among the four metabolic phenotype groups.”

11- In Table 1, please provide percent rather than numbers for sex distribution (just for male gender); please provide percent rather than numbers for smoking status, and each percent should be provided separately for Never-/Ex-/Current smoker.
In Table 1, information provided in the table for pack-years cigarette smoking is not clear at all.

In Table 1, please also indicate type of data provided for continuous and categorical variables.

Response
Thank you for your comments. According to your comments, we have revised the Table 1.

Table 2, needs to be revised for changing row and column; please provide HRs (95% CI) and P value for each phenotype by three model (i.e. crude model, model 1 and model 2). Furthermore, HR (95% CI) and P value for potential confounders should be removed from the table and provided in another table (or preferably in the text).

Response
Thank you for your suggestion. According to your suggestion, we have revised the Table 2 and HR (95% CI) and p value for potential confounders have provided in another table (Supplemental Table).

Figure 1, which contains important about study population and their follow up during the study period, should be revised according to STROBE Statement for flowchart of cohort studies. Please provide more details about numbers of participants were excluded from each cohort population (Metabolically healthy non-obesity, Metabolically healthy obesity, Metabolically abnormal non-obesity, Metabolically abnormal obesity).

Response
Thank you for your valuable comment. We have added follow up during the study period and also added more details about numbers of participants were excluded from each cohort population in Figure 1.

Discussion section critically needs to be revised. It is too short and main important issues that the authors were be supposed to discuss, have been neglected. In the first paragraph the authors need to be focused on main findings rather than emphasizing on novelty of this work. They also need to address the mentioned studies earlier in my comments, which investigate the association of metabolic syndrome and its components with risk of gastric cancer. As suggested for further analysis to indicate contribution of each metabolic abnormality in development of the outcome, related findings need to be discussed as well.

Response
Thank you for your valuable suggestion. According to your suggestion, we have revised the Discussion section (Page 10,11, Line 217-246 ).
“This cohort study of apparently healthy Japanese people is the first to reveal an association between MHO and incident gastric cancer. This study shows that individuals with MAO, but not those with MHO, had an elevated risk for incident gastric cancer. In addition, the presence of impaired fasting plasma glucose and/or diabetes, and hypertension were associated with elevated risk incident gastric cancer.

Obesity was a risk factor for incident gastric cancer [3], although the effect of obesity on gastric cancer was smaller than that on other obesity-related cancers. Previous studies revealed that the risk of incident colorectal cancer [12] and incident breast cancer [13], both of which have been shown to be related to obesity [4], was not high in subjects with MHO. In addition, another study revealed that the risk of obesity-related cancer in MHO was lower than that in MAO [31]. In fact, previous studies revealed the association between metabolic syndrome and incidence of gastric cancer [16-19].

As to why MAO, but not MHO, was associated with a higher risk of incident gastric cancer, there were several possible explanations. It has been reported that metabolic syndrome is associated with gastric cancer [16-19,32]. In this study, we showed that the presence of metabolic abnormalities, especially impaired fasting plasma glucose and/or diabetes and hypertension, were associated with gastric cancer, which was almost the same as previous studies [33,34]. Inflammation, as represented by elevation of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), is known to be closely associated with not only obesity [35], but also the metabolic abnormalities, including impaired fasting plasma glucose and hypertension [36]. Inflammation leads to the development of gastric cancer by stimulating proliferation and inhibiting apoptosis of human gastric cancer cells [37]. Formation of reactive oxygen species (ROS), by formation of advanced glycation end products [38], leads to DNA damage and development of gastric cancer. In addition, tumor cell progression is stimulated by enhancing the mTOR signaling pathways through an increase in insulin-like growth factor 1 (IGF-1) [39]. On the other hand, it has been reported that the levels of inflammation and IGF-1 in MHO were lower than those in MAO [40,41]. Collectively, these results could explain why the MAO phenotype, but not the MHO phenotype, was associated with a higher risk of incident gastric cancer.”


17- Selection bias that the authors addressed in the discussion ("because we only included the participants who were re-examined in the health-checkup program") needs more clarification.

Response

Thank you for your valuable comment. We have revised the limitation (Page 11, Line 249-250) described as below.

“First, there was a possibility of selection bias, because we only included the participants who were re-examined in the health-checkup program. There is a possibility that there is a characteristic difference between the participants who were re-examined in the health-checkup program and those who did not.”

18- Conclusion section needs to be revised to highlight clinical importance of the findings; the authors should contextualize their findings and provide major possible implications of the study results. How their study findings may contribute to screen at risk obese subjects?

Response

Thank you for your comment. According to your comment, we have revised the Conclusion section (Page 12, Line 263-264) described as below.

“In conclusion, our study showed that MAO individuals, not MHO individuals, had a higher risk of incident gastric cancer. Thus, to prevent future gastric cancer, we should focus more on the presence of metabolic abnormalities rather than obesity itself.”