PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of sarcopenia with ideal cardiovascular health metrics among US adults: a cross-sectional study of NHANES data from 2011 to 2018
AUTHORS	Chen, Weihua; Shi, Shanshan; Jiang, Yizhou; Chen, Kaihong; Liao, Ying; Huang, Rongchong; Huang, Kun

VERSION 1 – REVIEW

REVIEWER	Adineh, H Iranshahr University of Medical Sciences, Epidemiology and biostatistics
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	The manuscript discusses a topic of great relevance to public health, with regard to public health evaluation and planning. However, the study sample used is very selective, Introduction: Introduction is adequate. Methods: - According to author statements in introduction, Sarcopenia is associated with CVD. Authors excluded about 84 percent of subjects (17817) from initial cohort (21128) because of exclusion criteria (CVD, Cancer, …). So, that sarcopenia subjects with CVD became out of study. It lead to the 'selection bias' and low generalizability of study. - Authors describe the objective of performing DXA in cohort, and also reasons for not performing for some subjects. - In CVH metrics section, authors say that "to maximize the sample size, we used hemoglobin A1c (HbA1c) values" , Please provide description how it increases sample size? - Authors not presented any finding in other sections and tables by HbA1C. - NHANES is a cohort study with fallow up during a time period and measurements in different time, authors must to determine which measurement used (measurements at the start of the study or at the end the study).also, sampling method, times of fallow up, … - In statistical section, authors said that "we used multiple logistic regression analysis to assess the effect of a different number of ideal cardiovascular health metrics (ICVHMs) on the incidence of sarcopenia". Since 84 percent of initial cohort has been excluded, please explain is it reliable to

	estimate incidence? (while authors estimated Odds ratio not risk ratio). - Authors fail to mention about checking normal distribution. - Author should describe the association of Sex, Race, and Alcohol use with Sarcopenia. Results: - In the first paragraph, authors mentioned about prevalence (1.7 %, 40.1 % ,… for ideal diet criteria and smoking ,respectively...). Since the study sample (3311) is strongly selective, authors can't say "prevalence". I would suggest saying "frequency in present sample" - According to epidemiologic methods, it is require a random and representative sample to estimating prevalence. - The table 1 should cite to original article or website. - The table 2 should describe the characteristics of study sample stratified by their status to Sarcopenia. - Author must to report SD instead of SE for describing dispersion - It is important to use odds instead of risk.(estimated effect measure in present study is OR) - In figure 3 the estimated OR for ICVHMs > 5 and ICVHMs > 3 reported 0.12 and 0.42 ,respectively. In text of manuscript, these measures reported 0.15 and 0.47, respectively. Please explain that. - The table 3 it is not to be in full text. Authors mention just interaction. - I suggest to present UN-adjusted OR beside adjusted OR.

REVIEWER	Barrett, Sheila Northern Illinois University, Department of Nutrition, Dietetics and Hospitality Administration
REVIEW RETURNED	16-Mar-2022

GENERAL COMMENTS	Abstract Edit under participants- …those who could not diagnose Under secondary measures- … prevalence of sarcopenia as measured by… Introduction Informative and sets the stage and background need for this study. Good to match to the AHA 2020 health indicators. Heath metrics were clearly identified. Methods- clearly presented, procedure is well laid out and all variables are described adequately. Results Very in-depth analyses. Clearly presented by variables Page 17 – line 17- sentence is hanging, correct to say " similar trends were observed …… Page 17- line 19, lower case p for physical activity

	Figures could be more clearly presented. Discussion Orderly and succinct, captures the essence of the study.

VERSION 1 – AUTHOR RESPONSE

Responds to the reviewer1's comments:
Dr. H Adineh, Iranshahr University of Medical Sciences

The manuscript discusses a topic of great relevance to public health, with regard to public health evaluation and planning. However, the study sample used is very selective,
Respond：Special thanks to you for your good comment. The question of the selectivity of the study sample is answered in detail in the following questions.

Introduction:
Introduction is adequate.
Respond：Thank you for your confirmation!

Methods:
- According to author statements in introduction, Sarcopenia is associated with CVD. Authors excluded about 84 percent of subjects (17817) from initial cohort (21128) because of exclusion criteria (CVD, Cancer, …). So, that sarcopenia subjects with CVD became out of study. It lead to the 'selection bias' and low generalizability of study.
Respond：Thank you for your constructive comments. We are sorry that our inclusion and exclusion criteria raised questions for you. In fact, we excluded those with missing data for diagnostic cardiovascular health metrics and sarcopenia, which made up the majority of the excluded population, and only 16.9% of the exclusions regarding CVD and other co-morbidities. In the NHANES cohort, the population without diagnostic sarcopenia and the population without cardiovascular health metrics were sampled in a stratified manner, so that the selection bias was minimized by selecting appropriate weights. Indeed, our data selection bias is only due to the lack of co-morbidity data in the population, but we still cannot completely exclude the effect of selection bias, so we present it as a limitation in the limitations section. And we will make up for this defect in future population studies according to your suggestions.

Limitation section:
Finally, 84 percent of initial cohort has been excluded in this study, which will increase the variance of the odds ratio estimates. This can be improved when the larger dataset is available in the future. (Line 264-266, Page 22)

- Authors describe the objective of performing DXA in cohort, and also reasons for not performing for some subjects.
Respond：Indeed, we described the goals of performing DXA in the cohort and the reasons why some subjects do not perform DXA. These are available in the official NHANES authors' guideline.

- In CVH metrics section, authors say that "to maximize the sample size, we used hemoglobin A1c (HbA1c) values", Please provide description how it increases sample size?
Respond：Thanks to your suggestion, we have added how we increased the sample size in the methods section as follows.

Method section:
Although the AHA relies on fasting glucose to determine hyperglycemia, we use hemoglobin A1c (HbA1c) concentrations for two reasons. First, recent recommendations from the American Diabetes Association allow the use of HbA1c to diagnose diabetes. Second, a significant percentage of NHANES participants who took the test did not fast. Therefore, we used HbA1c values < 5.7%, 5.7%-6.4%, and > 6.5% as a proxy for fasting plasma glucose levels < 100 mg/dL, 100 to < 126 mg/dL, and > 126 mg/dL. (Line 128-131, Page 10)

- Authors not presented any finding in other sections and tables by HbA1C.
Respond：Thank you for your suggestion, as we only use HbA1C to determine whether the patient's blood glucose is on target, we do not think that further description of HbA1C is needed.

- NHANES is a cohort study with fallow up during a time period and measurements in different time, authors must to determine which measurement used (measurements at the start of the study or at the end the study).also, sampling method, times of fallow up, …
Respond：Thank you for your kind comment. We have completed the description of the NHANES database in the methods section and added the missing elements as described below.

Method section:
NHANES is a nationally representative health survey designed and administered by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). The NHANES was designed to represent the civilian non-institutionalized United States population using a complex multistage probability sampling methodology. We conducted a retrospective analysis of a cohort of US population of the NHANES from 2011 to 2018. The NHANES includes extensive demographic data, physical examinations, laboratory tests, health-related questionnaires and lists of prescription medications, which were measured at the start of the study. Further details on the data collection procedure and analytical guidelines are publicly available on the NHANES website. (Line 88-93, Page 6-7)

- In statistical section, authors said that "we used multiple logistic regression analysis to assess the effect of a different number of ideal cardiovascular health metrics
(ICVHMs) on the incidence of sarcopenia". Since 84 percent of initial cohort has been excluded, please explain is it reliable to estimate incidence? (while authors estimated Odds ratio not risk ratio).
Respond：Thanks for your comments! In this study, 84 percent of initial cohort has been excluded, while 55 percent is due to the CVH data missing caused from stratified sampling procedure of NHANES survey and 12 percent due to DXA data missing. Since the stratified sampling is to make the data more representative to the U.S population and independent of population’s health status, we think it is reasonable to assume little bias from these data missing, which accounts for most of the missing cases. On the other hand, the exclusion of large amount of data will increase the variance of the odds ratio estimates. That will improve when the larger dataset is available in the future. Therefore, we have added this part of the discussion in the Limitations section.

Limitation: Finally, 84 percent of initial cohort has been excluded in this study, which will increase the variance of the odds ratio estimator. This can be improved when the larger dataset is available in the future. (Line 264-266, Page 22)

- Authors fail to mention about checking normal distribution.
Respond：We are sorry for that we did not perform a test for normal distribution. Because we used Survey package in R software to analysis the data. However, there are no tests of normality in the survey package. And we also asked the author of the Survey package (professor of biostatistics, Thomas Lumley), and he give us two reasons for not being able to test the normal distribution of NHANES data, quote “The first is that no-one has worked out how to convert widely used normality

tests to complex sampling (eg, Shapiro-Wilk, Kolmogorov-Smirnov). The second is that none of the inference in the package is based on assumptions about the distribution of the data; it's all based on assumptions about the sampling." And based on these reasons, we reckon that normality test is not necessary.

- Author should describe the association of Sex, Race, and Alcohol use with Sarcopenia.
Respond：We describe the relationship between gender, race, alcohol consumption and sarcopenia, specifically in Table S1, and have added this section to the manuscript. The details are as follows.

Result section:
Sarcopenia was identified in 32.1% of 89 females based on the sarcopenia criteria and the Hispanic more like to develop sarcopenia (36.5%) compared with other races/ethnicities. Heavy use of alcohol did not show significant differences between both groups (P = 0.821). (Line 168-170, Page 12)

Results:
- In the first paragraph, authors mentioned about prevalence (1.7 %, 40.1 % ,… for ideal diet criteria and smoking ,respectively...). Since the study sample (3311) is strongly selective, authors can't say "prevalence". I would suggest saying "frequency in present sample"
Respond：Thank you for your kind comments, we are aware of the poor use of words, so we have corrected the word "prevalence" in the results section to "frequency in the present sample".

- According to epidemiologic methods, it is require a random and representative sample to estimating prevalence.
Respond：Thank you for your professional input, which plays an important role in the quality of our manuscripts. And we hope future studies would fulfill that.

- The table 1 should cite to original article or website.
Respond：Thanks to your kind comments. We have cited the original article in the table1.

- The table 2 should describe the characteristics of study sample stratified by their status to Sarcopenia.
Respond：Although our findings suggest that the CVH goal could be facilitated by controlling the prevalence of sarcopenia. However, our study explored whether different degrees of CVH could influence the prevalence of sarcopenia. Therefore, we still believe that the current baseline grouping does not need to be changed. However, based on your constructive comments, we have presented the table of groupings by sarcopenia status in the table S1 and in the manuscript.

Result section:
Moreover, we analyzed the characteristics of this study population by sarcopenic status. Sarcopenia was identified in 32.1% of 89 females based on the sarcopenia criteria and the Hispanic more like to develop sarcopenia (36.5%) compared with other races/ethnicities. Heavy use of alcohol did not show significant differences between both groups (P = 0.821). Furthermore, the patient with sarcopenia had poor education level, BMI risk, healthy diet score risk, blood pressure risk, fasting plasma glucose risk, and overall CVH metrics. And more detailed analyses are presented in Table S1. (Line 168-172, Page 12-13)

- Author must to report SD instead of SE for describing dispersion
Respond：Thank you for your suggestion, as we used weights inferred from the overall real-world US population, we should really use SE instead of SD, as verified by many previous renowned studies (1,2).

Reference:

1. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA internal medicine 2014;174:516-24.
2. Zhang Z, Jackson S, Merritt R, Gillespie C, Yang Q. Association between cardiovascular health metrics and depression among U.S. adults: National Health and Nutrition Examination Survey, 2007-2014. Annals of epidemiology 2019;31:49-56.e2.

- It is important to use odds instead of risk. (estimated effect measure in present study is OR)
Respond：Thank you for your suggestion, we have changed “risk” to “odds” in the results section of the manuscript.

- In figure 3 the estimated OR for ICVHMs > 5 and ICVHMs > 3 reported 0.12 and 0.42, respectively. In text of manuscript, these measures reported 0.15 and 0.47, respectively. Please explain that.
Respond：Thank you for your careful observation, and we apologize for the misunderstanding due to our error. We did not perform a detailed check of the figure during the version change after the data analysis and the values in the figure were incorrect. We have replaced the figure.

- The table 3 it is not to be in full text. Authors mention just interaction.
Respond：Thanks to your suggestion, we have provided a more detailed description of table3 in the results section as follows.

Result section:
Notably, the age group showed stronger association in the subgroup aged < 45 years (aOR: 0.35, 95% CI: 0.20-0.64, P < 0.001). And the association between intermediate or ideal CVH and sarcopenia was not significant in female and lower education level subgroups. Further, the effect of different ages was explored in the female subgroup. In the female participants < 45 years of age, intermediate or ideal CVH scores remained an independent protective factor for sarcopenia (aOR: 0.14, 95% CI: 0.05-0.40, P < 0.001; Table S2). Among subgroups of non-Hispanic Black and other ancestry, the odds of sarcopenia decreased by 75% in participants with intermediate or ideal CVH than in participants with poor CVH (aOR: 0.25, 95% CI: 0.07-0.88, P = 0.038; aOR: 0.24, 95%CI: 0.09-0.66, P = 0.008; Table 3). For all of subgroups, there was no significant interaction (all P for interaction > 0.05). (Line 184-191, Page 14)

- I suggest to present UN-adjusted OR beside adjusted OR.
Respond：Thanks for your suggestion, we show the un-adjust OR in the table, please check our modified version for details.

Result section:
The intermediate or ideal CVH was associated with an odds reduction of sarcopenia than poor CVH (odds ratio [aOR]: 0.34 0.21-0.54, P < 0.001; Table 3). (Line 180-181, Page 14)

Responds to the reviewer2’s comments:
Dr. Sheila Barrett, Northern Illinois University

Abstract
Edit under participants- …those who could not diagnose
Under secondary measures- … prevalence of sarcopenia as measured by…
Respond：Thank you for your suggestions, we are making changes in the abstract according to your comments.

Introduction
Informative and sets the stage and background need for this study. Good to match to the AHA 2020 health indicators.

Heath metrics were clearly identified.
Respond：Thank you for your confirmation!

Methods- clearly presented, procedure is well laid out and all variables are described adequately.
Respond：Thank you for your confirmation!

Results
Very in-depth analyses. Clearly presented by variables
Page 17 – line 17- sentence is hanging, correct to say " similar trends were observed ……
Respond：Thank you for your suggestions, we have made changes in the manuscript based on your comments.

Page 17- line 19, lower case p for physical activity
Respond：Thank you for your suggestions, we have made changes in the manuscript based on your comments.

Figures could be more clearly presented.
Respond：Thanks to your suggestion, we have revised and re-uploaded our figures.

Discussion
Orderly and succinct, captures the essence of the study.
Respond：Thank you for your confirmation!

VERSION 2 – REVIEW

REVIEWER	Adineh, H Iranshahr University of Medical Sciences, Epidemiology and biostatistics
REVIEW RETURNED	20-Jun-2022

GENERAL COMMENTS	The manuscript discusses a topic of great relevance to public health, with regard to public health evaluation and planning. However, the study sample used is very selective, Introduction: Introduction is adequate. Methods: - According to author statements in introduction, Sarcopenia is associated with CVD. Authors excluded about 84 percent of subjects (17817) from initial cohort (21128) because of exclusion criteria (CVD, Cancer, …). So, that sarcopenia subjects with CVD became out of study. It lead to the 'selection bias' and low generalizability of study.NO - Authors describe the objective of performing DXA in cohort, and also reasons for not performing for some subjects.OK - In CVH metrics section, authors say that "to maximize the sample size, we used hemoglobin A1c (HbA1c) values" , Please provide description how it increases sample size?OK - Authors not presented any finding in other sections and tables by HbA1C. NO

	- NHANES is a cohort study with fallow up during a time period and measurements in different time, authors must to determine which measurement used (measurements at the start of the study or at the end the study).also, sampling method, times of fallow up, … OK - In statistical section, authors said that "we used multiple logistic regression analysis to assess the effect of a different number of ideal cardiovascular health metrics (ICVHMs) on the incidence of sarcopenia". Since 84 percent of initial cohort has been excluded, please explain is it reliable to estimate incidence? (while authors estimated Odds ratio not risk ratio). NO - Authors fail to mention about checking normal distribution. - Author should describe the association of Sex, Race, and Alcohol use with Sarcopenia. Results: - In the first paragraph, authors mentioned about prevalence (1.7 %, 40.1 % ,… for ideal diet criteria and smoking ,respectively...). Since the study sample (3311) is strongly selective, authors can't say "prevalence". I would suggest saying "frequency in present sample" YES - According to epidemiologic methods, it is require a random and representative sample to estimating prevalence. - The table 1 should cite to original article or website. NO - The table 2 should describe the characteristics of study sample stratified by their status to Sarcopenia. - Author must to report SD instead of SE for describing dispersion OK - It is important to use odds instead of risk.(estimated effect measure in present study is OR). OK - In figure 3 the estimated OR for ICVHMs > 5 and ICVHMs > 3 reported 0.12 and 0.42 ,respectively. In text of manuscript, these measures reported 0.15 and 0.47, respectively. Please explain that. - The table 3 it is not to be in full text. Authors mention just interaction. - I suggest to present un-adjusted OR beside adjusted OR. OK

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. H Adineh, Iranshahr University of Medical Sciences

Responds to the reviewer1's comments:

Methods:

- According to author statements in introduction, Sarcopenia is associated with CVD. Authors excluded about 84 percent of subjects (17817) from initial cohort (21128) because of exclusion criteria (CVD, Cancer, …). So, that sarcopenia subjects with CVD became out of study. It lead to the 'selection bias' and low generalizability of study.NO

Respond：Thank you for your constructive comments. I'm apologizing for not understanding your opinion last time. After our team discussed again, we included participant who with CVD in the analysis to resolve the 'selection bias'. Furthermore, we re-cleaned the original dataset, which ended up with 9,326 participants included in the analysis. Therefore, the current excluded population is mainly due to the lack of DXA and physical data. With the weighted analysis, we believe that our selection bias has been controlled to the maximum extent possible. Meanwhile the results of the latest analysis are consistent with the previous ones, which proves the reliability of our findings.

- Authors describe the objective of performing DXA in cohort, and also reasons for not performing for some subjects.OK

Respond：Thank you for your confirmation of our revisions.

- In CVH metrics section, authors say that "to maximize the sample size, we used hemoglobin A1c (HbA1c) values", Please provide description how it increases sample size?OK

Respond：Thank you for your confirmation of our revisions.

- Authors not presented any finding in other sections and tables by HbA1C. NO

Respond：Thank you for your constructive comments. We have presented the HbA1C in the table 1 and the result section.

Result section

The frequency in the present sample of participants meeting the ideal level for the remainder of CVH metrics were cigarette smoking (weighted, 75.2%), HbA1c (weighted, 75.2%), total cholesterol level (weighted, 54.1%), blood pressure (weighted, 49.1%), physical activity (weighted, 41.9%), and BMI (weighted, 31.1%) (Table 1). (Line 166-169, Page 12)

- NHANES is a cohort study with fallow up during a time period and measurements in different time, authors must to determine which measurement used (measurements at the start of the study or at the end the study).also, sampling method, times of fallow up, … OK

Respond：Thank you for your confirmation of our revisions.

- In statistical section, authors said that "we used multiple logistic regression analysis to assess the effect of a different number of ideal cardiovascular health metrics

(ICVHMs) on the incidence of sarcopenia". Since 84 percent of initial cohort has been excluded, please explain is it reliable to estimate incidence? (while authors estimated Odds ratio not risk ratio). NO

Respond：Thanks for your comments! After resetting the inclusion exclusion criteria and re-cleaning the original dataset, the final analysis was included by 9,326 participants. Although a half of initial cohort has been excluded and estimated Odds ratio, the current excluded population is mainly due to the lack of DXA and physical data. The reasons for missing data in these two types are as follows: (i) missing physical data are mainly due to random missing, and (ii) missing DXA data are mainly due to resampling. Therefore, with the weighted analysis, it was also reliable to estimate incidence.

- Authors fail to mention about checking normal distribution.

Respond：We are sorry for that we did not perform a test for normal distribution. Because we used Survey package in R software to analysis the data. However, there are no tests of normality in the survey package. And we also asked the author of the Survey package (professor of biostatistics, Thomas Lumley), and he give us two reasons for not being able to test the normal distribution of NHANES data, quote “The first is that no-one has worked out how to convert widely used normality tests to complex sampling (eg, Shapiro-Wilk, Kolmogorov-Smirnov). The second is that none of the inference in the package is based on assumptions about the distribution of the data; it's all based on assumptions about the sampling.” And based on these reasons, we reckon that normality test is not necessary.

- Author should describe the association of Sex, Race, and Alcohol use with Sarcopenia.

Respond：We describe the relationship between gender, race, alcohol consumption and sarcopenia, specifically in Table S1, and have added this section to the manuscript. The details are as follows.

Results:

- In the first paragraph, authors mentioned about prevalence (1.7 %, 40.1 % ,… for ideal diet criteria and smoking ,respectively...). Since the study sample (3311) is strongly selective, authors can’t say "prevalence”. I would suggest saying "frequency in present sample" YES

Respond：Thank you for your confirmation of our revisions.

- According to epidemiologic methods, it is require a random and representative sample to estimating prevalence.

Respond：Thank you for your professional input, which plays an important role in the quality of our manuscripts. And we hope future studies would fulfill that.

- The table 1 should cite to original article or website. NO

Respond：Thanks to your kind comments. We have cited the original article in the table 1.

- The table 2 should describe the characteristics of study sample stratified by their status to Sarcopenia.

Respond：Although our findings suggest that the CVH goal could be facilitated by controlling the prevalence of sarcopenia. However, our study explored whether different degrees of CVH could influence the prevalence of sarcopenia. Therefore, we still believe that the current baseline grouping does not need to be changed. However, based on your constructive comments, we have presented the table of groupings by sarcopenia status in the table S1 and in the manuscript.

Result section:

Moreover, we analyzed the characteristics of this study population by sarcopenic status. Sarcopenia was identified in 45.9% of 403 females based on the sarcopenia criteria and the non-Hispanic white ancestry more like to develop sarcopenia (47.5%) compared with other races/ethnicities. Furthermore, the patient with sarcopenia had poor education level, BMI risk, healthy diet score risk, blood pressure risk, HbA1c risk, and overall CVH metrics. And more detailed analyses are presented in Table S1. (Line 176-180, Page 13)

- Author must to report SD instead of SE for describing dispersion OK

Respond：Thank you for your confirmation of our revisions.

- It is important to use odds instead of risk.(estimated effect measure in present study is OR). OK

Respond：Thank you for your confirmation of our revisions.

- In figure 3 the estimated OR for ICVHMs > 5 and ICVHMs > 3 reported 0.12 and 0.42, respectively. In text of manuscript, these measures reported 0.15 and 0.47, respectively. Please explain that.

Respond：Thank you for your careful observation, and we apologize for the misunderstanding due to our error. After the reanalysis, we checked and revised the manuscript and the figure.

- The table 3 it is not to be in full text. Authors mention just interaction.

Respond：Thanks to your suggestion, we have provided a more detailed description of table 3 in the results section as follows.

Result section:

Notably, the age group also showed stronger association in the subgroup aged < 45 years (aOR: 0.38, 95% CI: 0.27-0.52, P < 0.001). Further, among subgroups of non-Hispanic Black, the odds of sarcopenia decreased by 79% in participants with intermediate or ideal CVH than in participants with poor CVH (aOR: 0.21, 95% CI: 0.08-0.50, P = 0.038; aOR: 0.24, 95%CI: 0.09-0.66, P < 0.001; Table 3). For all of subgroups, there was no significant interaction (all P for interaction > 0.05), expect of education levels (P for interaction= 0.014). (Line 193-198, Page 15)

- I suggest to present un-adjusted OR beside adjusted OR. OK

Respond：Thank you for your confirmation of our revisions.

VERSION 3 – REVIEW

REVIEWER	Adineh, H Iranshahr University of Medical Sciences, Epidemiology and biostatistics
REVIEW RETURNED	01-Sep-2022

GENERAL COMMENTS	no comment