PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Links between arterial stiffness and bone mineral density in middle-aged and elderly Chinese individuals: a cross-sectional study
AUTHORS	Zhang, Meng; Bai, Lijuan; Kang, Jing; Ge, Jing; Peng, Wen

VERSION 1 – REVIEW

REVIEWER	Lan T Ho-Pham Bone and Muscle Research Group, Ton Duc Thang University, Vietnam.
REVIEW RETURNED	20-Apr-2019

GENERAL COMMENTS	Comments to authors This study is among the first investigation in to the association between BMD and CAVI among middle aged and elderly Chinese inpatients. However, I have some concerns on the materials and methods that could affect the authors' conclusion. I invite the authors to address the following points: Specific Comments 1. Although this study was a retrospective anonymous study, it should be approved by a research and ethics committee. This issue has to be cleared by the Journal. 2. All participants were inpatients who would have multiple comorbidities and were on multiple medications. Could the authors show more data concerning comorbidities and medications. 3. What is the rationale for classifying individuals into 50-59, 60-69 and >=70 age groups? 4. For measurement of BMD, the bilateral femoral neck was measured, but the results were shown for one side. Please clarify! What was the reproducibility of BMD measurement in your institution? 5. The association of CAVI and BMD with advancing age is obvious. In table 2, the authors may consider analyze the data stratify by gender. 6. It seems that the association between CAVI and THBMD varied according to the statistical models the authors used. Therefore, statistical analysis must be taken seriously, and in my vew the analysis should be redone. (a) Please provide a rationale for adjustment. Why did the authors adjust for history of CVD, history of DM, eGFR, etc. How were these data ascertained? It is not good enough to simply include everything in a regression model without a proper biologic justification. (b) I want to see a full report of regresson coefficients for each covariate in the regression model. I also want to know whether the regression assumptions are met.

Without a proper analysis, I cannot make sense of the data and conclusion.

7. In the presence of multiple adjustment, I suggest that a P < 0.005 be used as a threshold for declaring statistical significance (see Ioannidis, "the proposal to lower P value thresholds to 0.005", JAMA 2018).

8. This study found that BMI was negatively associated with CAVI in middle aged and elderly individuals while the previous studies have reported a negative association of obesity with vascular stiffening in children and adolescents but not in older adults and the elderly. The authors should explain that.

9. The sentence "In this population-based cross-sectional study…" in the conclusion of the abstract is not quite correct, because participants were inpatients.

REVIEWER	Joshua Barzilay Emory School of Medicine USA
REVIEW RETURNED	22-Apr-2019

GENERAL COMMENTS	The paper is of interest but there are certain issues that require clarification: 1. Why did you use CAVI? what advantage does it offer over simpler methods such as PWV or ankle brachial index? How does it correlate with traditional measures of peripheral artery disease such as a ABi or PWV?.. Also what is blood density? 2. In the INTRO you discuss how arterial stiffness is related to change in arterial structure. While of interest, there is no information about this in your study, and it is not relevant to this study which is about the relation of bone and arterial stiffness. Consider deleting this issue from the paper. 3. "When the ankle brachial index (ABI) is less than 0.9, the lower CAVI value cannot reflect the actual degree of arterial stiffness11, so we exclude individuals with an ABI value less than 0.9 on either side." How many people did you exclude? Was this enough to bias your results? 4. Were participants for this study sick people who were hospital for medical care [you write that you reviewed their medical records] or were these people invited to stay in hospital for medical testing for the purposes of this study? 5. The DISCUSSION section meanders quite a bit. The purpose of the paper is whether or not there is an association of BMD with a measure of arterial stiffness. Build the DISC around this, not around the association of CAVI with BMI or age. There is also quite a lot of speculation for which you have no evidence. Focus on the purpose of the paper

REVIEWER	Junli Zuo 1.Department of Hypertension, Ruijin Hospital North, Shanghai Jiao Tong University School of Medicine, Shanghai, China 2.Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	This is a cross-sectional study evaluating the association of BMD (bone mineral density) and arterial stiffness in middle-aged and elderly Chinese individuals. The finding that TH (the total hip) BMD was still associated with CAVI (the cardio-ankle vascular index) values after adjusting for confounding factors is of potential interest. However, the concerns listed below need to be addressed.

Abstract

1. Line 27. Please state the mean age for the whole cohort.
2. Line 42. Please change "association" to "correlation". Use the correct description of association, correlation, relationship etc in the whole text..
3. In addition, the authors should provide accurate description of whether the association is positive or negative or inverse such as line 54, TH BMD was still inversely associated with CAVI.
4. In adjusting for confounding factors, why adjust for effect of HDL instead of TC, TG, or LDL-C?
5. Line 10-31. It is not sufficient to state only the strengths of the study. At least one main limitation should also be added.

Introduction

1. Line 14-34 of page 4. The authors state that CAVI is widely used in the evaluation of cardiovascular disease and related risk factors for arterial stiffness. However, PWV is the gold standard for arterial stiffness, so please give the reason for the use of CAVI, such as being a pressure independent metric of arterial stiffness. There are many studies that investigate the relationship between arterial stiffness and BMD by using different methods. Masugata's study showed that elevated CAVI values are associated with reduced BMD in patients with hypertension. The study recruited patients from the geriatrics department who might have hypertension. So what is the difference between this study and other studies?

Methods

1. Line 20 of page 5. This is a retrospective study. Did it have ethics approval? This should be clearly stated.
2. Line 23 of page 5. Inclusion criteria state menopausal women, however the abstracts show both genders instead of only female.
3. Lines 35-41of page 5. When the ankle brachial index (ABI) is less than 0.9, the lower CAVI value cannot reflect the actual degree of arterial stiffness, so individuals with an ABI value less than 0.9 on either side are excluded. The number of subjects that were excluded should be given for ABI <0.9, but ABI>1.4 indicates presence of vascular calcification especially in diabetics, were they also excluded? Generally, ABI and baPWV were simultaneously measured by machine. This should be added to the ABI and baPWV measurement in the methods.
4. References should be given for the BMD and CAVI measurements, including method of measurement and also details of the number of measurements taken and assessment conditions.
5. Give the number of subjects with cardiovascular and cerebrovascular disease and how they were diagnosed..
6. The CKD-EPI formula is less common than the MDRD formula; why use this formula?

7. Clarify how age groups were defined in decades, including age>80 years?

Results

	1. Why adjust for qualitative variables such as history of DM instead of continuous variable such sugar level? And what about osteoporosis drugs, which influence the BMD? 2. Line 33 of page 8. The description of the sentence is inaccurate. 3. Please describe which figures show what results. **Discussion** 1. The authors should reorganize the discussion, concentrating on BMD and arterial stiffness. 2. Limitations of the study should be added, such as adjustments for osteoporosis drugs as a confounding factor. **Tables** 1. Table 2. Add the total subject characteristics, history of CVD and DM, sugar level and antihypertensive and osteoporosis drugs. Give details of NLR abbreviation and baPWV 2. Table 3. r = Pearson Correlation Coefficient, but history of CVD and DM is a qualitative variable and should be analyzed by Kendall's tau-b correlation instead of Pearson Correlation. Define NLR abbreviation.. 3. Table 4. Put all variables in the table and 95% CI including age, gender, BMI smoking, history of CVD, history of DM, SBP, HDL-C, blood uric acid, fibrinogen, eGFR. Moreover, suggest to adjust for the osteoporosis and antihypertensive medicine as confounding factors. Define eGFR abbreviation **Figures** 1. Please give the figure legends after the reference and mark the number of figures. Delete from figure 1 of page 20 to figure 3 of page 22. Please give the formula for the last figure and change the figure legend to make it clear.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Lan T Ho-Pham
Institution and Country: Bone and Muscle Research Group, Ton Duc Thang University, Vietnam.
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comments to authors
This study is among the first investigation in to the association between BMD and CAVI among middle aged and elderly Chinese inpatients. However, I have some concerns on the materials and methods that could affect the authors' conclusion. I invite the authors to address the following points:
Specific Comments

We thank the reviewer for the comments and feedback to improve the quality of the manuscript. We hope that our responses below would address the reviewer's concerns.

1. Although this study was a retrospective anonymous study, it should be approved by a research and ethics committee. This issue has to be cleared by the Journal.
Response: Yes, our study was approved by the ethics committee of tongji medical college, huazhong university of science and technology (No.2018S456). We can provide the electronic version of the approval. We highlight this point in the first paragraph of Study population of page 5.
2. All participants were inpatients who would have multiple comorbidities and were on multiple medications. Could the authors show more data concerning comorbidities and medications.

4

Response: Thanks for your suggestion. We think it's very good. For osteoporosis drugs, we excluded patients who were on estrogen replacement therapy, but there were no data about the use of bisphosphonates and other drugs. Unfortunately, comorbidities and other medications, such as anti-diabetes and anti-hypertension drugs, were not yet available. We plan to supplement this information in future studies.

3.   What is the rationale for classifying individuals into 50-59, 60-69 and >=70 age groups?

Response: According to your suggestion and literature review, we re-divided the population into three equal groups according to age as a new table 1. Compared with the original grouping method, the statistical significance of each age group did not change.

4.   For measurement of BMD, the bilateral femoral neck was measured, but the results were shown for one side. Please clarify! What was the reproducibility of BMD measurement in your institution?

Response: We did measure the BMD of the bilateral femoral neck. Then we took its average of the bilateral BMD in our study. The measurements of BMD in our institution were carried out by experienced professionals according to the instructions of the instrument after the prescribed quality control. So, we thought it had good reproducibility.

5.   The association of CAVI and BMD with advancing age is obvious. In table 2, the authors may consider analyze the data stratify by gender.

Response: Thanks for your suggestion. We added gender stratification as the new table 2.

6.   It seems that the association between CAVI and THBMD varied according to the statistical models the authors used. Therefore, statistical analysis must be taken seriously, and in my vew the analysis should be redone.

(a)   Please provide a rationale for adjustment. Why did the authors adjust for history of CVD, history of DM, eGFR, etc. How were these data ascertained? It is not good enough to simply include everything in a regression model without a proper biologic justification.

Response: Through regression analysis, we would find Age, BMI, CVD, DM, SBP, HDL-C, fibrinogen and eGFR were statistically significantly correlated with CAVI as following shown. Besides, according to our expertise, we known that gender, smoking and hyperuricemia were likely to affect arterial elasticity. So, we added gender, smoking and UA in the final model, although they were not statistically significantly correlated with CAVI.

Coefficients of regression

variable	Unstandardized Coefficients		Standardized Coefficients β	t	p
	B (95% CI)	Std. Error			
age	0.072(0.065 to 0.079)	0.004	0.631	19.58	<0.001
BMI	-0.068(-0.098 to -0.038)	0.015	-0.18	-4.406	<0.001
CVD	0.69(0.482 to 0.898)	0.106	0.261	6.511	<0.001
DM	0.62(0.415 to 0.825)	0.104	0.24	5.935	<0.001
SBP	0.026(0.021 to 0.032)	0.003	0.36	9.263	<0.001
HDL-C	-0.592(-0.916 to -0.268)	0.165	-0.148	-3.59	<0.001
fibrinogen	0.186(0.062 to 0.311)	0.063	0.123	2.934	0.003
eGFR	-0.027(-0.032 to -0.022)	0.003	-0.394	-10.292	<0.001

Dependent Variable: CAVI

(b) I want to see a full report of regression coefficients for each covariate in the regression model. I also want to know whether the regression assumptions are met.

Without a proper analysis, I cannot make sense of the data and conclusion.

Response: Our study met the regression assumptions. The normal P-P plot of CAVI, ANOVA of the regression equation, R^2 of the regression equation, Durbin-Watson value and collinearity diagnosis were shown as following. Besides, the full report of regression coefficients for each covariate in the regression model were added in table 4 of my manuscript.

Normal P-P Plot of CAVI
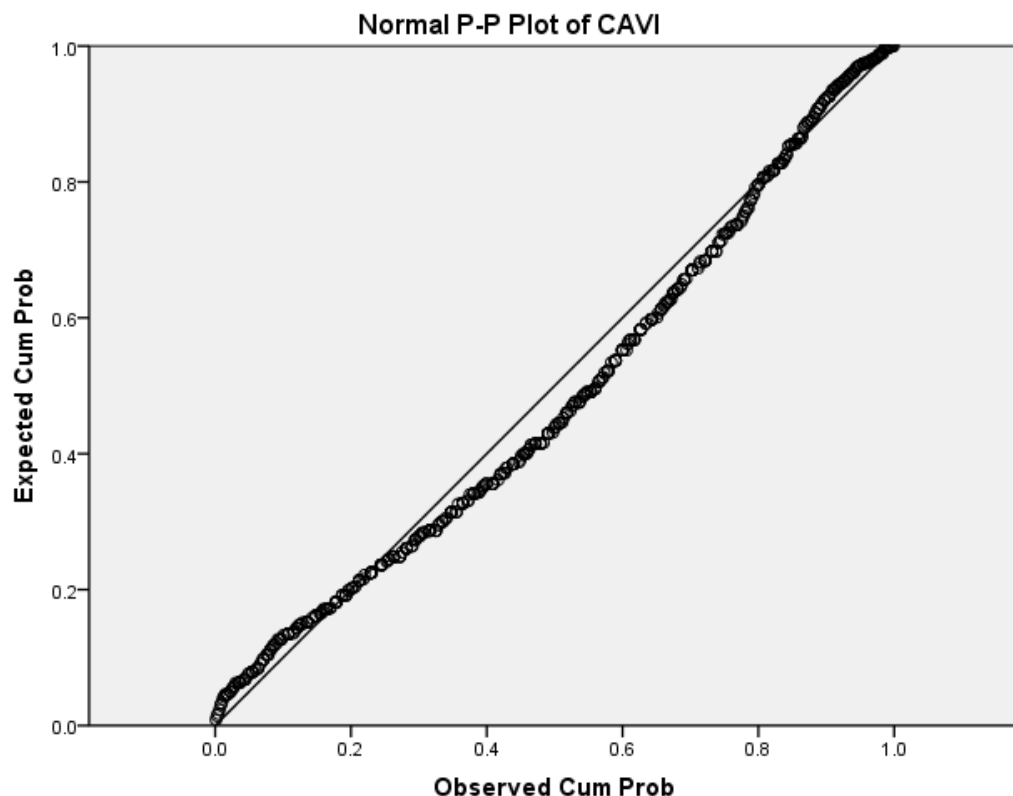
ANOVA

Model 3		Sum of Squares	df	Mean Square	F	p
TH BMD	Regression	484.978	12	40.415	48.628	<0.001
	Residual	455.442	548	0.831		
	Total	940.42	560			
FN BMD	Regression	481.611	12	40.134	47.936	<0.001
	Residual	458.808	548	0.837		
	Total	940.42	560			
LS BMD	Regression	479.125	12	39.927	47.432	<0.001
	Residual	461.294	548	0.842		
	Total	940.42	560			

a. Predictors: (Constant), age, gender, BMI, smoking, CVD, DM, SBP, HDL-C, UA, fibrinogen, eGFR, BMD

b. Dependent Variable: CAVI

Model Summary

Model 3	R	R^2	Adjusted R^2	Std. Error of the Estimate	Durbin-Watson
TH BMD	0.718	0.516	0.505	0.91165	1.974
FN BMD	0.716	0.512	0.501	0.91501	1.967
LS BMD	0.714	0.509	0.499	0.91748	1.966

a. Predictors: (Constant), age, gender, BMI, smoking, CVD, DM, SBP, HDL-C, UA, fibrinogen, eGFR, BMD

b. Dependent Variable: CAVI

Collinearity Statistics

Exposure	Tolerance	VIF	Tolerance	VIF	Tolerance	VIF

age	0.414	2.415	0.406	2.46	0.436	2.293
gender	0.547	1.828	0.574	1.743	0.55	1.819
BMI	0.8	1.249	0.846	1.182	0.803	1.245
smoking	0.737	1.358	0.737	1.357	0.74	1.351
CVD	0.854	1.171	0.855	1.17	0.857	1.167
DM	0.841	1.189	0.841	1.189	0.85	1.177
SBP	0.848	1.179	0.849	1.178	0.848	1.179
HDL-C	0.841	1.189	0.841	1.189	0.843	1.186
UA	0.659	1.518	0.659	1.518	0.659	1.517
fibrinogen	0.897	1.115	0.897	1.115	0.897	1.115
eGFR	0.436	2.291	0.437	2.29	0.434	2.304
TH BMD	0.628	1.592				
FN BMD			0.674	1.484		
LS BMD					0.674	1.483

Dependent Variable: CAVI

7. In the presence of multiple adjustment, I suggest that a P < 0.005 be used as a threshold for declaring statistical significance (see Ioannidis, "the proposal to lower P value thresholds to 0.005", JAMA 2018).

Response: We think your suggestion is excellent. We have read the proposal, and agree with your view of lowering P threshold to 0.005. We will explain the statistical significance of the results modestly.

8. This study found that BMI was negatively associated with CAVI in middle aged and elderly individuals while the previous studies have reported a negative association of obesity with vascular stiffening in children and adolescents but not in older adults and the elderly. The authors should explain that.

Response: In our study, we found BMI was weakly negatively associated with CAVI. In bivariate correlation analysis, r= -0.18, p<0.001. In multiple linear regression analysis, coefficients B= -0.077 (-0.102 to -0.052), p<0.001. Studies shown that lean mass was negatively correlated with arterial stiffness, while fat mass was positively correlated with arterial stiffness (Benetos A, Effects of lean and fat mass on bone mineral density and arterial stiffness in elderly men. doi: 10.1007/s00198-008-0807-8.). But our study and most of the studies, diagnosed obesity solely by weight or waist circumference. These were not accurate. In future, we need to measure the amount of fat mass and lean mass in patients to explore the association between CAVI and fat mass and lean mass in different age groups, rather than mixing them together.

9. The sentence "In this population-based cross-sectional study…" in the conclusion of the abstract is not quite correct, because participants were inpatients.

Response: That has been modified in the conclusion of the abstract.

Reviewer: 2
Reviewer Name: Joshua Barzilay
Institution and Country: Emory School of Medicine   USA
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

The paper is of interest but there are certain issues that require clarification:

We thank the reviewer for the overall positive review and comments.

1. Why did you use CAVI? what advantage does it offer over simpler methods such as PWV or ankle brachial index? How does it correlate with traditional measures of peripheral artery disease such as a ABI or PWV? Also, what is blood density?

Response: PWV is the gold standard for arterial stiffness. However, blood pressure at the time of measurement can affect the CAVI value. CAVI has unique advantages over PWV and ABI. CAVI does not depend on blood pressure changes during the measurements. Besides, CAVI could represent the stiffness of the arterial tree from the origin of the aorta to the ankle. ABI mainly reflects the narrowing rather than stiffness of blood vessels. In the early stages of arterial stiffness, the ABI is likely to be normal because the vessels have not narrowed. There are many elderly patients with hypertension in our population. Many people have high blood pressure when measuring the degree of arterial stiffness. So CAVI was chosen in our study. Blood density is the mass of 1 liter of blood (blood density=mass/volume). Besides, it has been recomposed in the third paragraph of introduction.

2. In the INTRO you discuss how arterial stiffness is related to change in arterial structure. While of interest, there is no information about this in your study, and it is not relevant to this study which is about the relation of bone and arterial stiffness. Consider deleting this issue from the paper.

Response: Thank you for your suggestion. That has been modified in the INTRO. We wrote this paragraph to illustrate the significance of measurement of arterial stiffness. But as you said, the purpose of this study is to explore the relationship between CAVI and BMD. So, we modified this section to make it more focused and coherent in context.

3. "When the ankle brachial index (ABI) is less than 0.9, the lower CAVI value cannot reflect the actual degree of arterial stiffness11, so we exclude individuals with an ABI value less than 0.9 on either side." How many people did you exclude? Was this enough to bias your results?

Response: We excluded 21 individuals with ABI value less than 0.9 on either side from a total of 605 individuals. We thought that not enough to produce a significant bias. Besides, we added Supplementary file 1.   Allocation process in our manuscript.

4. Were participants for this study sick people who were hospital for medical care [you write that you reviewed their medical records] or were these people invited to stay in hospital for medical testing for the purposes of this study?

Response: Participants for this study were sick people who were hospital for medical care.

5. The DISCUSSION section meanders quite a bit. The purpose of the paper is whether or not there is an association of BMD with a measure of arterial stiffness. Build the DISC around this, not around the association of CAVI with BMI or age. There is also quite a lot of speculation for which you have no evidence. Focus on the purpose of the paper

Response: It has been recomposed in the DISSCUSSION.

Reviewer: 3
Reviewer Name: Junli Zuo
Institution and Country: 1. Department of Hypertension, Ruijin Hospital North, Shanghai Jiao Tong University School of Medicine, Shanghai, China 2. Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia
Please state any competing interests or state 'None declared': I have no competing interests in relation to the work described.

Please leave your comments for the authors below
This is a cross-sectional study evaluating the association of BMD (bone mineral density) and arterial stiffness in middle-aged and elderly Chinese individuals. The finding that TH (the total hip) BMD was still associated with CAVI (the cardio-ankle vascular index) values after adjusting for confounding factors is of potential interest. However, the concerns listed below need to be addressed.

We thank the reviewer for the comments to improve the quality of our manuscript. We hope that our responses below would address the reviewer's concerns.

Abstract

1. Line 27. Please state the mean age for the whole cohort.

Response: It has been added in the abstract.

2. Line 42. Please change "association" to "correlation". Use the correct description of association, correlation, relationship etc in the whole text.

Response: It has been revised in the text.

3. In addition, the authors should provide accurate description of whether the association is positive or negative or inverse such as line 54, TH BMD was still inversely associated with CAVI.

Response: It has been revised in the abstract.

4. In adjusting for confounding factors, why adjust for effect of HDL instead of TC, TG, or LDL-C?

Response: Regression analysis of CAVI with these components was performed separately. But after adjusting for age, only HDL-C was statistically correlated with CAVI as shown following. We all know that age is a common factor affecting blood lipids and CAVI. So, we choose HDL-C rather than other components.

Lipids	Coefficients	p
HDL-C	-0.406(-0.659 to -0.153)	0.002
LDL-C	0.012(-0.082 to 0.105)	0.808
TC	-0.03(-0.11 to 0.051)	0.466
TG	0.052(-0.29 to 0.133)	0.209

5. Line 10-31. It is not sufficient to state only the strengths of the study. At least one main limitation should also be added.

Response: It has been recomposed.

Introduction

1. Line 14-34 of page 4. The authors state that CAVI is widely used in the evaluation of cardiovascular disease and related risk factors for arterial stiffness. However, PWV is the gold standard for arterial stiffness, so please give the reason for the use of CAVI, such as being a pressure independent metric of arterial stiffness. There are many studies that investigate the relationship between arterial stiffness and BMD by using different methods. Masugata's study showed that elevated CAVI values are associated with reduced BMD in patients with hypertension. The study recruited patients from the geriatrics department who might have hypertension. So what is the difference between this study and other studies?

Response: As you said, PWV is the gold standard for arterial stiffness. However, blood pressure at the time of measurement can affect the CAVI value. CAVI does not depend on blood pressure changes during the measurements. Besides, CAVI could represent the stiffness of the arterial tree from the origin of the aorta to the ankle. There are many elderly patients with hypertension in our population. Many people have high blood pressure when measuring the degree of arterial stiffness. So CAVI was chosen in our study. Besides, it has been recomposed in the third paragraph of introduction.

The difference between this study and other studies: Firstly, many studies focus on the correlation between PWV and BMD have been conducted in the United States, Europe, or Japan. We are targeting Chinese people. Second, we selected middle-aged and elderly inpatients, and did not specifically screen the population, because the prevalence of chronic diseases in the elderly is very high, this is a real-world study. Finally, for the first time in our population, we used CAVI as an index of arterial stiffness.

Methods

1. Line 20 of page 5. This is a retrospective study. Did it have ethics approval? This should be clearly stated.

Response: Yes, our study was approved by the ethics committee of tongji medical college, huazhong university of science and technology (No.2018S456). We can provide the electronic version of the approval. We highlight this point in the first paragraph of Study population of page 5.

2. Line 23 of page 5. Inclusion criteria state menopausal women, however the abstracts show both genders instead of only female.

9

Response: Our study included postmenopausal women over the age of 50 and men over the age of 50.

3. Lines 35-41of page 5. When the ankle brachial index (ABI) is less than 0.9, the lower CAVI value cannot reflect the actual degree of arterial stiffness, so individuals with an ABI value less than 0.9 on either side are excluded. The number of subjects that were excluded should be given for ABI <0.9, but ABI>1.4 indicates presence of vascular calcification especially in diabetics, were they also excluded? Generally, ABI and baPWV were simultaneously measured by machine. This should be added to the ABI and baPWV measurement in the methods.

Response: We excluded 21 individuals with ABI value less than 0.9 on either side from a total of 605 individuals. And there was no individual with ABI> 1.4 in our people. We added the measurement of ABI in the part of Measurement of the CAVI and ABI. Besides, we added Supplementary file 1. Allocation process to describe the participants' enrolment and reasons for exclusion in our manuscript.

4. References should be given for the BMD and CAVI measurements, including method of measurement and also details of the number of measurements taken and assessment conditions.

Response: It has been recomposed in the part of Measurement of the CAVI and ABI in our manuscript.

5. Give the number of subjects with cardiovascular and cerebrovascular disease and how they were diagnosed.

Response: The total number of people suffering from cardiovascular and cerebrovascular disease was 233. They were diagnosed through the medical history report of patients with proof of their records of coronary angiography or brain MRI/CT examination.

6. The CKD-EPI formula is less common than the MDRD formula; why use this formula?

Response: An article published by Inker LA on the New England journal of medicine found that the combined creatinine-cystatin C equation performed better than equations based on either of these markers alone in 2012. And all of our patients tested creatinine and cystatin C when they admitted. So, we use CKD-EPI creatinine-cystatin C formula to calculate eGFR. (Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-9. doi:10.1056/NEJMoa1114248)

7. Clarify how age groups were defined in decades, including age>80 years?

Response: The age range of the population we studied was 50 to 94 years. According to your suggestion and literature review, we re-divided the population into three equal groups according to age as a new table 1. Compared with the original grouping method, the statistical significance of each age group did not change.

Results

1. Why adjust for qualitative variables such as history of DM instead of continuous variable such sugar level? And what about osteoporosis drugs, which influence the BMD?

Response: Thanks for your suggestion. We think it's very good. For osteoporosis drugs, we excluded patients who were on estrogen replacement therapy, but there were no data about the use of bisphosphonates and other drugs. We plan to supplement this information in future studies.

2. Line 33 of page 8. The description of the sentence is inaccurate.

Response: It has been revised in the new manuscript.

3. Please describe which figures show what results.

Response: It has been described in the new manuscript.

Discussion

1. The authors should reorganize the discussion, concentrating on BMD and arterial stiffness.

Response: It has been recomposed in the DISSCUSSION.

2. Limitations of the study should be added, such as adjustments for osteoporosis drugs as a confounding factor.

Response: It has been recomposed in the Limitations.

Tables

1. Table 2. Add the total subject characteristics, history of CVD and DM, sugar level and antihypertensive and osteoporosis drugs. Give details of NLR abbreviation and baPWV

Response: It has been modified according to your suggestion in the new table1. However, there was no information about drugs and baPWV in our data. We hope to make further supplement in the future research.

2. Table 3. r = Pearson Correlation Coefficient, but history of CVD and DM is a qualitative variable and should be analyzed by Kendall's tau-b correlation instead of Pearson Correlation. Define NLR abbreviation.

Response: Thank you for your suggestion, which has been revised.

3. Table 4. Put all variables in the table and 95% CI including age, gender, BMI smoking, history of CVD, history of DM, SBP, HDL-C, blood uric acid, fibrinogen, eGFR. Moreover, suggest to adjust for the osteoporosis and antihypertensive medicine as confounding factors. Define eGFR abbreviation

Response: Your suggestion is very good. We added all variables and 95% CI in table 4. However, we unable to supplement comorbidities and medications for reasons of time and permissions. We plan to supplement this information in future studies.

Figures

1. Please give the figure legends after the reference and mark the number of figures. Delete from figure 1 of page 20 to figure 3 of page 22. Please give the formula for the last figure and change the figure legend to make it clear.

Response: It has been revised.

VERSION 2 – REVIEW

REVIEWER	Lan T Ho-Pham Bone and Muscle Research Group, Ton Duc Thang University, Vietnam.
REVIEW RETURNED	22-Jun-2019

GENERAL COMMENTS	The revised manuscript is sufficient quality for publication in the BMJ Open.

REVIEWER	Junli Zuo 1. Department of Geriatric Medicine Ruijin Hospital North Shanghai Jiaotong University School of Medicine, China 2. Honorary Senior Research Fellow Department of Biomedical Sciences, Faculty of Medicine and Health Sciences Macquarie University, Sydney, Australia
REVIEW RETURNED	26-Jun-2019

GENERAL COMMENTS	The authors have addressed my previous comments