Author's response to reviews

Title: Association of calcaneal quantitative ultrasound parameters with metabolic syndrome in middle-aged and elderly Chinese: A large population-based cross-sectional study

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Author’s response to reviews: see over
Dear Editor and Reviewers:

Thank you for your comments concerning our manuscript entitled “Association of calcaneal quantitative ultrasound parameters with metabolic syndrome in middle-aged and elderly Chinese: A large population-based cross-sectional study” (ID: 1530650141847143). Those comments are very helpful. We have revised the manuscript (parts which have been changed are in red font) carefully according to the comments and have answered all the questions one by one. We hope those corrections will make the paper suitable for the journal. Please check the revised manuscript uploaded lately as well as the answers (blue font) below.

Responses to the reviewers’ comments:

Reviewer In Joo IJ Kim:

1. Why the authors did not include the information about T or Z score, and estimated BMD? Wasn’t it significant? The information needs to be added to the Table 2

   Considering the reviewer’s suggestion, we have added the information about T-score and BMD in Table 2. We found that BMD was also lower in postmenopausal women with MS than those without before or after age adjustment. No difference regarding T-score was found before any adjustment between the groups in postmenopausal women, while the association was significant after age adjustment.

2. p3.

   In China, a nationwide epidemiological survey from 1997 to 1999 showed that based on bone mineral density (BMD) of vertebra and femur neck measured by dual energy X-ray absorptiometry (DXA), the prevalence of osteoporosis in Chinese over 40 years old was 19.9% for women and 11.5% for men, respectively[6].

   # The sentence is awkward. China is repeated in one sentence. This need to be corrected.

   We’ve corrected the language flaw and marked the corresponding part red in the new manuscript (page 3).

3. p7. 3.3 Fragile fractures

   Why don’t you estimate the factors that can predict fragile fracture such as QUS parameters in vertebral or non-vertebral fracture, respectively? In your reference, Cargo study, the risk factors for vertebral or non-vertebral fracture were different. And is there any reason that you didn’t separate the risk factors for premenopausal women and postmenopausal women? Wasn’t there any difference?

   We have re-written this part according to the reviewer’s suggestion. Significant relationships were detected between age, SOS and non-vertebral fractures in men and postmenopausal women (table 4), while no association was found regarding MS status. Besides, age was found as a risk factor for vertebral fractures [OR=1.095(1.012-1.185), p=0.024 in men, OR=1.065(1.010-1.122), p=0.019 in postmenopausal women]. There was no risk factor for vertebral or non-vertebral fractures in premenopausal women (page 7). The main purpose of our study was to investigate the relationship between QUS parameters and MS, the analysis of osteoporosis fractures was only an additional part, so the information on fractures were only collected by questionnaires instead of source documents and radiology examinations. These limitations have already been mentioned in the discussion part of the paper.
4. p7. 3.4. 25(OH)D levels

In postmenopausal women, we randomly chose 1739 subjects to have their serum 25(OH)D measured. We found that postmenopausal women with MS had lower 25(OH)D levels than those without (42.31 ± 14.07nmol/L vs. 44.95 ±14.63nmol/L, P<0.001), and the difference remained after age and BMI adjustment. In women with vitamin D deficiency [25(OH)D<50nmol/L], the prevalence of MS was 54%, which was significantly higher than those without vitamin D deficiency (47.8%).

# To assess the value of the 25(OH)D, it is need to inform the season of the sampling period. The variation must be large enough to diminish the significance between two groups. The difference is only 16.8ng/dL vs. 17.9ng/dL. Is it really meaningful the 1ng/dL differences to judge the vitamin D deficiency?

Considering the reviewer's suggestion, we have informed the season of the sampling period in page 7 in red. Samples for 25(OH)D evaluation were collected during September to November (autumn in Nanjing). Our result showed that postmenopausal women with MS had lower vitamin D level than those without. Although the difference was small, it is statistically significant. The purpose was not to diagnose whether the subjects were vitamin D deficient or not, but to analyze whether vitamin D level was an underlying reason for the QUS results.

5. p7-8

Since on one hand QUS is a more convenient and somehow different way for evaluating bone characteristics compared with DXA, on the other hand, MS represents a major health problem nowadays, more information provided by our study will help to understand the pathogenesis of metabolic bone disease further.

# The sentence is awkward.

Revised portion are marked in red in the paper (page 8).

6. p8

MS is a cluster of disorders including abdominal obesity, impaired glucose tolerance, hypertension and dyslipidemia, since each component has certain complicated impact on bone metabolism, taking together, the influence of MS on QUS becomes complicated.

# This is already described at introduction. You do not need to repeat the same content.

The repeat content was deleted.

7. p8

In our study, the relationship between MS and QUS differs between genders and between menopause statues. We did not found any relationship between MS and QUS in men and premenopausal women, which coincides with the Camargo cohort study[13] and the Taiwan study[14] about QUS, and also in agreement with previous studies with DXA[17].

# In Camargo and Taiwan study, the subjects were postmenopausal women and men. In those studies, there were no relationship between metabolic syndrome and bone metabolism. In this study, there were some relationship between metabolic syndrome and bone metabolism in postmenopausal women. The reason why there were some differences exist needs to be discussed.

In postmenopausal women, Taiwan study found no relationship, Camargo study showed the
positive relationship while we found an adverse effect of MS on QUS. In our study, MS diagnostic criterion was defined according to recommendations generated by IDF in 2005. According to this criterion, WC was the first requirement for the diagnosis of MS. So we think MS has an effect on QUS, in which WC plays an important role. As WC was negatively related to QUS, so we concluded that the effect on QUS by MS was negative. We can also find in table 2 that, after age, BMI and WC adjustment, the difference of QUS parameters between postmenopausal women with MS and those without was disappeared.

8. p10error?
Fragile fractures are the severe consequence of osteoporosis, leading to the increase of disability and mortality
# severe??
We are very sorry for our negligence of spelling. Revised portion are marked in red in the paper (page 10).

9. p11
Thus, the QUS parameters might be different.
# Different from what? QUS parameters and fracture had no relationship? Or the differences between the time that fracture occurred and the time when QUS are measured? What is your point?
We meant the differences between the time that fracture occurred and the time when QUS are measured (page 11).

10. Tables 1, 2, 3
There are no explanations about the abbreviations.
We have made correction according to the reviewer’s comments.

11. p11
According to Hamann et al[26], BMD is increased in T2DM, in theory, this should be associated with a decreased risk of fractures, but the opposite is seen. So the prediction of osteoporosis and fractures by QUS or DXA could be controversial. This might be the reason for our finding.
# Why the authors mentioned about the T2DM? This study and the others references about the metabolic syndrome and QUS parameters, or prevalent fractures. This study did not include any data or subgroup analysis about T2DM. This paragraph obscured the main results.
We did not mean to analyses T2DM. The point of the paragraph is to emphasize that the prediction of osteoporosis and fractures by QUS could be controversial. We hypothesized that MS might lead to bone mineral loss while have no effect on fractures (page 11).

Reviewer Darko Kastelan:
1. The major drawback of the study is inconsistency of the results. Moreover, conclusions could not be drawn from the results. Namely, authors conclude that metabolic syndrome has detrimental effect on bone mass. However, only component of metabolic syndrome that was negatively associated with QUS parameters was waist circumference whereas all others (FPG, BMI, SBP, TG) showed positive relationship. Furthermore, associations between metabolic syndrome and QUS parameters were significant only for SOS in postmenopausal women. Nevertheless, significance of
this association disappeared after controlling for age, BMI and WC.

It is really true as reviewer pointed out that the only component of metabolic syndrome that was negatively associated with QUS parameters was waist circumference whereas all others (FPG, BMI, SBP, TG) showed positive relationship. However, MS diagnostic criterion used in our study was defined according to recommendations generated by IDF in 2005. According to this criterion, WC was the first requirement for the diagnosis of MS. So we think MS has an effect on QUS, in which WC plays an important role. As WC was negatively related to QUS, so we concluded that the effect on QUS by MS was negative. Considering the reviewer’s suggestion, we have included the information about T-score and BMD in Table 2. We found that BMD was also lower in postmenopausal women with MS than those without before or after age adjustment.

2. Clinical and biochemical characteristics of the cohort of postmenopausal women are missing (Table 1).
In Table 2 there is no data for Model 3 (adjustment for age, BMI, WC and alcohol consumption).
Missing portions are marked in red in the paper.

Thank you very much for your comments and suggestions, we really appreciate all the help. Looking forward to hearing from you.

Best regards.

Yours sincerely,

Mengdie Cao