Author's response to reviews

**Title:** Low cardiorespiratory fitness is associated with metabolic syndrome independent of physical activity in Hong Kong Chinese midlife women

**Authors:**

Ruby Yu (rubyyu@cuhk.edu.hk)
Forrest Yau (forrest@cuhk.edu.hk)
Suzanne C Ho (suzanneho@cuhk.edu.hk)
Jean Woo (jeanwoowong@cuhk.edu.hk)

**Version:** 2  **Date:** 11 March 2013

**Author's response to reviews:** see over
Dear Editor

Below is my response to reviewers.

Version: 1 Date: 2 February 2013
Reviewer: Patricia Hageman
Reviewer's report:

1) The stated purpose is to determine the relative and combined associations of PA and CRF with the prevalence of MS and it is meritorious to have CRF assessments completed using a symptom-limited maximal exercise test. The statistical analysis dichotomized the data for fitness based on tertiles. The values of the tertiles were not published, leaving no reference to the cut-off point to support the group as “unfit”. It would seem that the cut-score from the low tertile for your sample would not be congruent with the ACSM guidelines or the authors own recently published, but not cited, article on normative data for cardiorespiratory fitness which includes information about the 50th percentile for women of similar age as in this manuscript [Yu R et al. 2011, Cardiorespiratory fitness and its association with body composition and physical activity in Hong Kong Chinese women aged from 55 to 94 years, Maturitas, 69:348-353].

Ans: Thanks for your comments. The ranges corresponding to the tertiles of VO_{2max} were: low tertile <21.2 ml/kg/min, middle tertile 21.2 - <24.3 ml/kg/min, high tertile ≥24.3 ml/kg/min. The low tertile of the sample was congruent with those in our previous published paper [Yu et. 2011]. The cutoff values have been included and the reference paper has been added. Please refer to the following or page 11 lines 19-21.

...the ranges corresponding to the tertiles of VO_{2max} were: low tertile <21.2 ml/kg/min, middle tertile 21.2 - <24.3 ml/kg/min, high tertile ≥24.3 ml/kg/min.

2) Please explain your use of the total index (TI) as opposed to the weighted total index (WTI) for the modified Chinese Baecke questionnaire in your analysis. In reviewing the cited reference which appears to be the work of the authors of this manuscript [31-Table 4], the TI was found to have poor correlation with mean energy expenditure from the 3 day diary for women and the WTI index had a significant correlation with mean energy expenditure from the 3 day diary for women. In reference [31-Table 6], the WTI appeared significant for mean energy expenditure per tertile of modified Chinese Baecke scores for women and the TI did not appear significant per tertile of modified Chinese Baecke scores for women. The reference [31] indicates that the WTI takes into account the estimated time spent and energy expenditure for each category of activity.
and data supported the validity of WTI as a measure of PA in Chinese women whereas the TI score did not.

Ans: Thanks for your comments. Yes, according to the previous publication of the Baecke questionnaire [37], weight total index (WTI) was found to have a higher correlation with mean energy expenditure than total index (TI). However, in this sample of postmenopausal women, we found that TI was normally distributed while WTI was skewed. Furthermore, TI has a higher correlation with MS than with WTI. Although WTI has taken into account for the different time and activity pattern of workers and housewives, the majority of subjects were worked as housewife (71.7%) and therefore we decided to use TI as opposed to WTI in the analysis.

3) The discussion includes relevant points; yet more information is needed throughout this section about the specific populations to which this study’s results are being compared. For example, you did cite page 14, lines 14-18 and again on page 16, line 7, that your findings are consistent with that of middle aged men (Caucasian?); however, on page 15, paragraph 1, you have not clarified the populations of the studies cited so that the reader can discern how your cohort results are similar to or different from other populations - which is important as related to the stated relevance of this work.

Ans: Thanks for your comments. The discussion has been revised. Please refer to the following or page 15 line 13 to page 17 line 13.

Our findings are generally consistent with extensive research that has documented the inverse associations of PA and MS. [14,15,17,18,23,25] However, after adjustment for CRF, the association between PA and MS observed in our study became attenuated. In stratified analyses, no significant association of PA with the prevalence of MS was observed within unfit or fit categories. These findings must be interpreted with cautions given the imprecise measurement associated with self-reported PA because self-reported data are more prone to recall bias and misclassification. Furthermore, the lack of statistical significance is likely explained by the small number of MS in fit subjects (n = 5). However, Laaksonen et al. [14] reported that middle-aged men without MS who complied with the PA recommendations had reduced risk of developing MS by about one-half compared with those engaging in no more than 60 minutes of moderate exercise per week, independent of CRF. The Medical Research Council (MRC) Ely Study showed that PA remained associated with MS and its progression after
adjustment for CRF. [17,18] It has also been shown that increasing levels of PA may protect against MS even in the absence of improved CRF. [23] The disparate findings may be due to the use of different PA measurements, in that PA was measured objectively with individually calibrated heart rate against energy expenditure in the MRC Ely Study, which is more precise compared with self-report data; and this may partially explain the relative stronger association found between PA and MS compared with CRF. However, in contrast to this notion, several studies have stated that leisure-time PA not resulting in an increase in CRF may not provide any protective effect on cardiovascular disease or its risk factors. [44,45] Results from the Aerobics center longitudinal study also demonstrated that the association of PA with all-cause mortality was eliminated after controlling for CRF. [46] Therefore, the independent role of PA on risk of MS is not confirmed. It is reasonable to suggest that the lower levels of CRF that are normally associated with PA are at least partially responsible for our findings.

Our results also agree with previous cross-sectional [24] and longitudinal studies [26] suggesting that low CRF is an independent risk factor of MS. Based on the baseline data of the Dose-Responses to Exercise Training Study (DR’s EXTRA), older men and women aged 57-79 years who were in the lowest tertile of VO$_{2\text{max}}$ had 10-fold higher risks of having MS compared with those in the highest tertile. [24] Based on the baseline and 2-year follow-up data of the same study, those who were in the highest tertile of baseline VO$_{2\text{max}}$ were 68% less likely to develop MS than those in the lowest tertile. [26] To check whether CRF contribute to the risk of MS independently of PA, PA was further adjusted and the association between CRF and MS remained significant, with subjects who were fit had 69% lower risk of MS. However, the MRC Ely Study showed contradictory results, with the association of CRF with MS attenuated after adjustment for objectively measured PA. [17] Therefore, whether the CRF effects on risk reduction for MS risk differ between PA levels is not firmly established.

The mechanisms by which moderate-to-high CRF provides a beneficial effect on the metabolic risk still need to be determined but it is reasonable to believe that the benefit may be largely mediated by components of MS. A previous study in 297 apparently healthy men showed that the high CRF group had lower triglyceride levels and higher HDL cholesterol levels than the low-or moderate-CRF groups, independent of abdominal subcutaneous and visceral fat. [20] The finding of this study showing the
independent association between CRF and MS for a given level of BMI lends further support to this observation.

Minor Essential Revisions (3)

1) The authors indicate that the relevance and importance of their work is that the “combined contributions of PA and CRF with MS are unclear” and that “further study is required in Chinese” as the majority of works in this area are related to Caucasians. With that perspective, more information is needed in the introduction for background about whether the problems and prevalence of metabolic syndrome in the Chinese population is similar to that of Caucasian or other populations. Providing more information from your reference [6] and perhaps other references would be appropriate to strengthen your rationale for the importance of this work. [eg. Cai H, Huang J, Xu G, Yang Z, Liu M, et al. (2012) Prevalence and Determinants of Metabolic Syndrome among Women in Chinese Rural Areas. PLoS ONE 7(5): e36936. doi:10.1371/journal.pone.0036936]. This will strengthen their stated relevance of this work.

Ans: Thank you very much for your advices. The background has been revised. Suggested reference has been added: reference [34]. Please refer to the following or page 4 lines 6-7 and page 5 lines 7-19.

The prevalence of MS increases with age [5], and is highly prevalent among midlife women, with the rates varying from 23.2 to 35.1%. [6-9]

Although several studies have simultaneously examined PA and CRF with MS, [14,15,17,18,23,25] the independent roles of both PA and CRF with MS are less firmly established. The combined contributions of PA and CRF with MS are less studied. Although in a previous population-based study, middle-aged men with both sedentary lifestyle and poor CRF were associated with increased risk of MS, [15] this study has been carried out among Caucasians, who may differ significantly from Chinese in terms of lifestyle, diet, and body physiology. For example, the age-defined VO$_{2\text{max}}$ was noted to differ between Chinese adult men and women and their age-matched Caucasians adults. [31] Previously we have examined the normative values of CRF in Chinese midlife and elderly women whereas similar VO$_{2\text{max}}$ values were observed as those of same sex and comparable age in Western populations, the VO$_{2\text{max}}$
values approximated the 5-15\textsuperscript{th} percentile values from the norms of the Cooper Institute. [32,33]
Yet the prevalence of MS in Chinese women is high, [34] therefore, further study is required in Chinese.

2) The authors note that age-defined fitness is lower in Chinese men and women compared with Caucasians which supports the importance of this work – however the authors did not reference findings from their recent 2011 work specific to providing normative values of cardiorespiratory fitness for women of similar age published in Maturitas; nor does the reader know how much lower the cardiorespiratory fitness values for these women relative to ACSM guidelines or other standards were. Addressing this will strengthen the rationale for the importance of this work.

Ans: Thank you very much for your advice. The background has been revised. Suggested reference has been added: reference [32]. Please refer to the following or page 5 lines 15-19.

Previously we have examined the normative values of CRF in Chinese midlife and elderly women whereas similar VO\textsubscript{2max} values were observed as those of same sex and comparable age in Western populations, the VO\textsubscript{2max} values approximated the 5-15\textsuperscript{th} percentile values from the norms of the Cooper Institute. [32,33] Yet the prevalence of MS in Chinese women is high, [34] therefore, further study is required in Chinese.

3) The authors need to review their article throughout for minor editorial corrections. Examples include:

p 5, line 16, “intakes” should read “intake”

Ans: “intakes” has been replaced by “intake”. Please refer to page 6 line 1.

p 10, line 1, need period behind the word “assessment”

Ans: “period” has been added behind the word “assessment” Please refer to page 11 line 1.
p 15, line 18, insert verb “occur” between the words “may” and “through”

Ans: “occur” has been added between the words “may” and “through” Please refer to page 17 line 18.
The authors of this manuscript aimed to investigate the relative and combined associations of physical activity and cardiorespiratory fitness with the prevalence of metabolic syndrome in midlife women. This is clearly study, which in terms of the experimental design is well conceived and controlled. The study results are not surprising or particularly innovative, but bring something more to the understanding of the relationship CRF-PA-MS in a specific population with different lifestyle and nutritional habits and a lower prevalence of MS than others countries. As the authors address, a limitation of the study is the fact that Physical Activity was assessed by means of questionnaires and not with more objective techniques like accelerometers (e.g. Actigraph system). Moreover, the final sample size is relatively small to reach strong conclusions.

There are some major concerns regarding the manuscript in its current form which I feel need addressing.

**Major Points:**

1. The prevalence of MS is extremely lower when compare to other samples from other countries (this aspect should be addressed by the authors). This condition make also that the comparisons between the re-categorized groups by MS precise a Effect Size estimation (i.e. Cohen’s d [95% exact confidence interval]).

Ans: Thanks for your comments. The discussion has been modified and the prevalence of MS and its implication have been discussed. Please refer to the following or page 18 line 16 to page 19 line 2 for the prevalence comparisons and page 15 lines 19-20, page 18 lines 8-10, and page 19 lines 21-23 for the limitation.

Several studies have reported the prevalence of MS among midlife women, from 23.2 to 35.1% across different populations. [6-9] The prevalence in Chinese women is also high, [34] in that people of Asian origin tend to accumulate more body fat and develop cardiovascular risk factors at a lower BMI levels or smaller waist circumference than Caucasians. [50] However, the prevalence of MS in our study (27.1%) was lower than that reported from an earlier study in China. In the study of 181 postmenopausal women conducted in 2006-2008, the prevalence of MS was 33.7%. [9] Variation in the prevalence of MS could be due to heterogeneity of population characteristics such as age distribution, socioeconomic status or nutritional status, or due to different genetic background.
Furthermore, the lack of statistical significance is likely explained by the small number of MS in fit subjects (n = 5)…Perhaps the small sample size of metabolically abnormal and obese subjects (n=10) attenuated the statistical power…The sample size was small and the cross-sectional design also does not allow us to infer a causal relationship of PA and CRF with MS.

2. The sample is relatively small, especially in the regression (please explain the lack of subjects because they do not fill the supposed total sample size of 158 women). In this case, please address it as limitation of the study as well as the total simple size.

Ans: Yes, this point has been added in the discussion and limitation. Please refer to the following or page 15 lines 19-20, page 18 lines 8-10, and page 19 lines 22-23.

Furthermore, the lack of statistical significance is likely explained by the small number of MS in fit subjects (n = 5)…Perhaps the small sample size of metabolically abnormal and obese subjects (n=10) attenuated the statistical power…The sample size was small and the cross-sectional design also does not allow us to infer a causal relationship of PA and CRF with MS.

Minor points:
1. I think the authors abuse of abbreviations (e.g. FBG, SBP, DBP)

Ans: The abbreviations of FBG, SBP, DBP etc. have been cancelled throughout the manuscript.

2. Please, define Waist circumference (WC) in the method section

Ans: Waist circumference has been defined. Please refer to the following or page 8 lines 17-18.

Waist circumference was measured over the abdomen at the smallest diameter between the costal margin and iliac crest
3. Why did the authors decide to use the Baecke questionnaire instead of the IPAQ?

Ans: We used Baecke questionnaire because we have modified, translated, and validated it in the Hong Kong Chinese adult population. Based on the original Baecke questionnaire that was divided into three parts (work, sport, and leisure time), a section assessing activities on housework has been included. Additional cultural-specific leisure time activities such as window shopping and playing mahjong, popular activities in Hong Kong, were included to make the questionnaire applicable for use in the Hong Kong Chinese adults of a wide age range. Furthermore, the reference period of the Baecke questionnaire is of the past year which is longer compared with the IPAQ.

4. Did the authors analyze the Normality of the data? Why did the authors employ T-student test to compare women with MS vs. healthy women? Why the authors did not adjust the model for age, and therefore performed an ANCOVA to contrast the main groups?

Ans: Yes, exposure of interests (PA and CRF) as well as BMI were normally distributed. Please see below histograms. The model (Table 1) has also been adjusted for age by using ANCOVA. Please refer to the following or page 11 lines 14-16.

Student t tests / Chi square tests were performed to compare subjects with MS and without MS. Analysis of Covariance (ANCOVA) was also performed after adjustment for age.
Histogram of VO$_{2\text{max}}$

Mean = 22.76
Std. Dev. = 3.756
N = 184
Histogram of PA total index

Mean = 9.07
Std. Dev. = 1.454
N = 188
5. Could you include the P derived of the regression analysis in the result sections?

Ans: Yes, P values have been included in the result section. Please refer to pages 13-14.

6. I miss a reference to the new concept of “metabolically healthy but obese phenotype”, especially when talking about cardiorespiratory fitness (Ortega et al., 2012). To further analyze and categorize by this aspect could enrich the manuscript and the discussion section. Ortega FB., Lee DC., Katzmarzyk PT., Ruiz JR., Sui X., Church TS., & Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J. 2012.
Ans: Thanks for your advice. This concept has been incorporated into the manuscript. Subjects were also categorized into four groups on the basis of absence or presence of MS and BMI levels of less than 25 kg/m$^2$ or at least 25 kg/m$^2$ (MS-O-, MS-O+, MS+O-, and MS+O+). In this sub-analysis, the waist circumference was excluded as a criterion in the definition of MS, since the purpose was to examine the CRF level across metabolic profile regardless of their adiposity. Comparisons of CRF level were made between the four categories using ANCOVA, with adjustment for age, dietary total calories intake, and PA. Pairwise comparisons were adjusted for the Bonferroni correction. The results have been discussed. The suggested reference (Ortega et al., 2012) has been included in the manuscript: reference [29]. Please refer to the following or page 12 lines 8-14 for statistical analysis; page 14 lines 15-21 for results; and page 18 lines 6-14 for discussion.

Statistical analysis: Subjects were also categorized into four groups on the basis of absence or presence of MS and BMI levels of less than 25 kg/m$^2$ or at least 25 kg/m$^2$ (MS-O-, MS-O+, MS+O-, and MS+O+). In this sub-analysis, the waist circumference was excluded as a criterion in the definition of MS, since the purpose was to examine the CRF level across metabolic profile regardless of their adiposity. Comparisons of CRF level were made between the four categories using ANCOVA, with adjustment for age, dietary total calories intake, and PA. Pairwise comparisons were adjusted for the Bonferroni correction.

Results: A decreasing trend in the level of CRR was observed across the four MS/BMI categories (P for trend <0.0001). After adjustment for age, dietary total calories intake, and PA, metabolically healthy and normal weight (MS-O-) subjects had a higher CRF level than metabolically healthy but obese (MS-O+) subjects (P=0.028) and metabolically abnormal obese (MS+O+) subjects (P=0.004). However, no significant differences were observed between metabolically healthy but obese (MS-O+) subjects and their metabolically abnormal and obese (MS+O+) peers (Figure 1).
Discussion: In contrast with previous studies showing a higher CRF level among metabolically healthy but obese subjects than their metabolically abnormal and obese peers, [29,49] we did not observe differences in level of CRF between the two groups in this study. Perhaps the small sample size of metabolically abnormal and obese subjects (n=10) attenuated the statistical power. However, there appears to be trend of a decreasing CRF levels across the MS/BMI categories, regardless of age, dietary total calories intake, and PA. Therefore, the findings of this study lend some support to the previous literature on the role of CRF on the risk of MS, and suggest that public health guidelines may need to be modified by placing more emphasis on the CRF level, especially for the midlife women.

7. I did not consider measuring clinical data on cardiovascular risk factors as a strength of this study due to the fact that MS can just be defined through these measurements.

Ans. Thanks. This has been deleted in the limitation. Please refer to the following or page 19 lines 20-21.

There are some limitations in this study. The subjects were not representative of the Hong Kong population, in that their education level was higher. PA was self-reported, which may be subject to recall bias. The sample size was small and the cross-sectional design also does not allow us to infer a causal relationship of PA and CRF with MS.
The authors investigated the cross-sectional relative and combined associations of PA and CRF with the risk of MS in a population-based sample of Hong Kong Chinese midlife women. They concluded that both PA and CRF were associated with the prevalence of MS but the latter appeared to be a better indicator with MS.

This manuscript is potentially interesting, however, there are a number of issues that should be addressed and clarified in order to increase the significance of the work.

My main concern is that the assessment of PA is self-reported. The behavior of physical activity is difficult to measure, and self-reported PA is subject to recall bias and misclassification. On the other hand, CRF can be measured objectively, using laboratory techniques. This may explain the relatively weaker associations found between MS and PA than with CRF.

Ans: Thanks for your comments. Yes, Self-reported PA is subject to recall bias and misclassification. This has been discussed in the manuscript. Please refer to the following or page 4 lines 21-23 for background and page 15 lines 17-19 and page 19 lines 6-9 for discussion.

**Background:** Compared with self-reported PA, CRF is a more accurate [28] and is thought to be stronger as a predictor of health outcomes because CRF is less prone to misclassification.

**Discussion:**

These findings must be interpreted with cautions given the imprecise measurement associated with self-reported PA because self-reported data are more prone to recall bias and misclassification...It is recognized that VO\textsubscript{2max} is an accurate measure of CRF and an objective measure of recent patterns of PA, which is less prone to misclassification than self-reported PA, and this may partially explain the relatively weaker associations found between MS and PA than with CRF in this study.
In title# The study findings are only in part original. Some of the results (ref.10,11,13,20) had been already reported in previous studies. The authors should specify that your population is Chinese, and that CRF is associated with MS better than (or independent of) PA. These points are main strength of this study.

Ans: The title has been amended. The new title is “Low cardiorespiratory fitness is associated with metabolic syndrome independent of physical activity in Hong Kong Chinese midlife women”.

In abstract# typing errors. Line 21 CRP

Ans: Thanks. It has been amended. Please refer to abstract.

Intable1, column heads# w/oMS, w/MS The authors should explain these abbreviations.

Ans: Thanks. ‘w/o’ has been replaced by ‘without’ and ‘w’ by ‘with’. Please refer to Table 1.
The overall goal of the present study is to examine the relative and combined associations of physical activity (PA) and cardiorespiratory fitness (CRF) with the prevalence of metabolic syndrome (MS) in midlife women. According to the authors, both PA and CRF were associated with the prevalence of MS but the latter appeared to be a better indicator with MS; therefore CRF should be encouraged in unfit individuals and especially among those who are sedentary to reduce risk of having MS and considered in the development of future primary risk assessment. The topic and some results of the present study are potentially interesting, but I could not find a strong scientific impact through the review of this manuscript.

The first, meta-analysis of 23 sex-specific cohorts of physical activity or physical fitness representing 1,325,004 person-years of follow-up clearly showed the dose-response relationship between physical activity, physical fitness and the risks of coronary artery disease and cardiovascular disease (Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc. 33:754-61, 2001.). It has been clear that additional amounts of physical activity or increased physical fitness levels provide additional health benefits. In addition, it has been clear that high physical fitness has increased the sensitivity for relative risk of atherosclerotic cardiovascular disease (RR=0.11-0.66) compared to high physical activity (RR=0.45-1.42). Secondly, the measurement accuracy of physical activity is inferior to that of physical fitness in quality because an assessment of physical activity is using by questionnaire method, but to measure the physiological parameter such as VO2max. The difference in result between physical activity and physical fitness may be partly a reflection of this measurement accuracy.

Ans: Thanks for your comments. The study results are not surprising, but add to the understanding of the relationship PA-CRF-MS in a specific population with different lifestyle and nutritional habits and a lower prevalence of MS than others countries. Furthermore this study specifically addresses the metabolic syndrome rather than cardiovascular diseases. For example, the age-defined VO2max was noted to differ between Chinese adult men and women and their age-matched Caucasians adults. [31] Previously we have examined the normative values of CRF in Chinese midlife and elderly women whereas similar VO2max values were observed as those of same sex and comparable age in Western populations, the VO2max values approximated the 5-15th percentile values from the norms of the Cooper Institute. [32,33] Yet directly measured
VO$_{2\text{max}}$ has been less studied in Chinese, particularly among midlife women; while the prevalence of MS in Chinese women is high, [34] therefore, further study is required in Chinese. Please refer to the following or page 5 lines 7-19.

Although several studies have simultaneously examined PA and CRF with MS, [14,15,17,18,23,25] the independent roles of both PA and CRF with MS are less firmly established. The combined contributions of PA and CRF with MS are less studied. Although in a previous population-based study, middle-aged men with both sedentary lifestyle and poor CRF were associated with increased risk of MS, [15] this study has been carried out among Caucasians, who may differ significantly from Chinese in terms of lifestyle, diet, and body physiology. For example, the age-defined VO$_{2\text{max}}$ was noted to differ between Chinese adult men and women and their age-matched Caucasians adults. [31] Previously we have examined the normative values of CRF in Chinese midlife and elderly women whereas similar VO$_{2\text{max}}$ values were observed as those of same sex and comparable age in Western populations, the VO$_{2\text{max}}$ values approximated the 5-15$^{\text{th}}$ percentile values from the norms of the Cooper Institute. [32,33] Yet the prevalence of MS in Chinese women is high, [34] therefore, further study is required in Chinese.

Based on the other reviewers’ advices, further analyses have been performed for the CRF level across the MS/body mass index (BMI) categories, a new concept of “metabolically healthy but obese phenotype” (Ortega FB., Lee DC., Katzmarzyk PT., Ruiz JR., Sui X., Church TS., &Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J. 2012) to enrich the manuscript and the discussion section. Although we did not observe differences in level of CRF between the metabolically healthy but obese subjects than their metabolically abnormal and obese peers, there appears to be trend of a decreasing CRF levels across the MS/BMI categories, regardless of age, dietary total calories intake, and PA. Therefore, the findings of this study lend some support to the previous literature on the
role of CRF on the risk of MS, and suggest that public health guidelines may need to be modified by placing more emphasis on the CRF level, especially for the midlife women. Please refer to the following or page 18 lines 6-14.

In contrast with previous studies showing a higher CRF level among metabolically healthy but obese subjects than their metabolically abnormal and obese peers, [29,49] we did not observe differences in level of CRF between the two groups in this study. Perhaps the small sample size of metabolically abnormal and obese subjects (n=10) attenuated the statistical power. However, there appears to be trend of a decreasing CRF levels across the MS/BMI categories, regardless of age, dietary total calories intake, and PA. Therefore, the findings of this study lend some support to the previous literature on the role of CRF on the risk of MS, and suggest that public health guidelines may need to be modified by placing more emphasis on the CRF level, especially for the midlife women.

We have also addressed the lower prevalence of MS of the study population in the discussion. Please refer to the following or page 18 line 16 – page 19 line 2.

Several studies have reported the prevalence of MS among midlife women, from 23.2 to 35.1% across different populations. [6-9] The prevalence in Chinese women is also high, [34] in that people of Asian origin tend to accumulate more body fat and develop cardiovascular risk factors at a lower BMI levels or smaller waist circumference than Caucasians. [50] However, the prevalence of MS in our study (27.1%) was lower than that reported from an earlier study in China. In the study of 181 postmenopausal women conducted in 2006-2008, the prevalence of MS was 33.7%. [9] Variation in the prevalence of MS could be due to heterogeneity of population characteristics such as age distribution, socioeconomic status or nutritional status, or due to different genetic background.
Finally, the suggested reference (Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc. 33:754-61, 2001.) has been included in the manuscript: reference [13].

Thank you very much.

Yours sincerely,

Ruby Yu