Author’s response to reviews

Title: ASSOCIATION BETWEEN CARDIORESPIRATORY FITNESS AND METABOLIC RISK FACTORS IN A POPULATION WITH MILD TO SEVERE OBESITY

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Reviewer reports:

C.J. Lavie (Reviewer 1): This is a well-done study and nicely written manuscript that reviews the impact of cardiorespiratory fitness (CRF) on metabolic risk factors in obesity. I have only minor comments to improve this fine paper:

Comment 1. The authors should include the most recent Flegal paper showing that class III or "morbid" obesity now has a prevalence of almost 8% in the US adult population (Flegal KM et al JAMA 2016;315:2284-2291);

Response - Thank you for this suggestion. As this was Canadian data, we elected to add the Twells reference to make it more relevant indicating that moderate/severe obesity is now ~5% in Canada (page 3, reference #9). The Flegal paper unfortunately does not report the prevalence of class II obesity separately, and so we are unable to generate an equivalent figure for the U.S.

Comment 2. A recent major paper on fitness versus fatness could be included (McAuley P et al American Journal of Medicine 2016;129:960-965);

Response - Thank you. This is now included in the introduction (ref #5).
Comment 3. Recent State of the Art reviews on this topic could be included (Lavie CJ et al Prog Cardiovasc Dis 2016;58:537-547 and Oktay AA et al Prog Cardiovasc Dis 2017;60:30-44);

Response - Thank you. These are now included in the introduction (ref 3+4).

Comment 4. A recent paper showing that physical activity that increases heart rate significantly lowers cardiometabolic risk factors, even in those with high sedentary times, could be included (Zisko N et al Prog Cardiovascular Dis 2017;60:89-95).

Response - Thank you for the suggestion. This is a nice reference, but the focus is not directly relevant to the study as we did not examine sedentary habits. As such it was a bit tough to weave into the discussion.

Heini Wennman (Reviewer 2): Review of manuscript OBSY-D-17-00078

The authors present their article with the title "Associations between cardiorespiratory fitness and metabolic risk factors in a population with mild to severe obesity". The topic is very interesting and important and it constitutes a relevant issue in the current society. The population studied represents the targeted group i.e. persons with higher degree of obesity and the sample size is good. Availability to data on cardiorespiratory fitness from a maximal exercise test strengthens the study. However, there are some severe limitations in the paper that I encourage the authors to give careful consideration and therefore I do not support a publication of the manuscript.

Response – Thank you for recognizing the importance of our work and for your constructive criticisms in improving our work. We have made substantial revisions that we hope have clarified our methods and have satisfied your concerns.

Comment - The title is appealing and clear, but when it comes to the introduction and the aims of the study it seems that there is a lack in the focus and the arguments to support this study are not fully convincing. It is suggested that the authors revise the order of the text in the introduction, and also clarify the content to more clearly present what is known and what still needs to be known on the topic to make a more solid claim for their study. For example, there has been a discussion "Fat or Fit" going on in the literature for a while already, and this could be good to highlight also in the introduction. It is also advisable that the authors avoid using the term "effect" in the text, particularly in the abstract, since this gives a notion about causality which is not studied in this current cross-sectional design.
Response – thank you for your suggestion. We have eliminated the use of the word ‘effect’ in referring to our findings and have hopefully revised the introduction to make our point more clear (page 3).

“The fit-fat paradox has been the topic of investigation for many years [1-5]. Specifically, it is suggested that individuals with mild obesity and a high fitness may not present with the typically expected negative health factors associated with obesity and may have lower risk of mortality than their normal-weight unfit counterparts [1-5].....”

Comment - The most severe limitation of the manuscript is the methods and the conclusions. Currently the figures, the results and the conclusion of the paper do not seem to match and the final conclusions even feel wrong relative to the data that is presented. Simply, for the reader to understand what has been done methods are too briefly presented and more details need to be given about the statistical testing. It seems from the figures that ANOVA testing with least square means has been applied and that many pairwise comparisons also have been made. However, it is not enough to state in the methods only that Least Squares means were used. All the essential information regarding the testing needs to be reported to the readers. As a consequence, when there is not enough information about the statistical tests, it is hard to understand the results only based on the figures and it seems that the figures and the presented conclusions do not match. This implies that the authors have made wrong interpretations of the results. As an example, the authors state that: "In females, a trend towards greater benefits of fitness on HDL in those with severe than mild obesity was seen (p=0.0581)." However, based on the figure, the magnitude of the difference between fit and unfit groups in different obesity categories cannot be concluded on. Furthermore, the BMI*Fitness interaction term that shows a borderline significance for HDL in women (p=0.0581), only describe that the association between fitness and HDL is not similar in across BMI groups, not the trend either over BMI or fitness. The authors conclude that the association between fitness and health may be similar if not augmented in individuals with severe obesity as compared to mild obesity but the figures do not support such a conclusion because it is not possible to see if the difference between unfit and fit groups is bigger or smaller in some obesity group than another. The only significant pairwise comparisons between unfit and fit group seems to be regarding HDL in the severe obesity group and regarding WC in moderate and severe obesity in women.

Response – We apologize for our lack of detail in our analysis and have substantially elaborated our statistical method on page 5. In the revision we have excluded the overweight patients who were inadvertently included in the dataset. As such, some of the results are subtly different and the sample is reduced from 904 to 853. We first examined the main effects and interaction effects of fitness and obesity group on the risk outcomes with obesity groups as a continuous variable. When the interaction term was significant (now only waist in women), this allowed us to determine that the association between obesity groups and waist was different between fitness
groups. Specifically as reflected in figure 2, the association between obesity group and WC in women was stronger in unfit than fit, such that the differences between the fit and unfit groups were magnified with increasing obesity group.

“There was a significant BMI x fitness interaction, indicating that the differences in waist circumference between fitness groups were greater in those with higher obesity classes in men (P=0.06) and women (P=0.0005). However, the difference in waist circumference between fitness groups only attained significance in the moderate (Fit versus Unfit: 112.1 versus 116.5 cm, P=0.001) and severe (Fit versus Unfit: 119.6 versus 129.2 cm, P<0.0001) obesity groups in women.” (page 6, paragraph 3).

Further, within obesity class, we only observe differences by fitness in the severe obesity groups for the relative risk for pre-clinical hypertension.

This is what we base our conclusion suggesting the benefits of fitness may be augmented in severe obesity. In the vast majority of analyses we observe no significant interaction which suggests that the association between fitness and health is similar between obesity groups. We hope that this clarifies how we have come to our conclusion that the association between fitness and health may be similar if not augmented in individuals with severe obesity as compared to mild obesity.

Comment - Because the sample is a selected clinical population consisting of obese subjects who have attended a Medical Clinic perhaps in order to receive treatment for their obesity, the analysis approach of the paper may need to be reconsidered. Instead of averages, maybe it would be better to look at the influence of fitness on the risk of having a poor instead of good level of the different metabolic risk factors? Looking at table 1 and also the figures, it seems that the participants to most part have a stable metabolic profile. As an example, the average blood pressure is above 130/80 mmHg only in the unfit-severe obese group. Based on the mean values it seems that medication plays an important role here and how the impact of medication is best dealt with in this sample needs careful consideration. It is not reported how many of the participants were/are on medications for blood pressure, lipids or diabetes even if the authors state that they control their models for medication.

Response – Thank you for the suggestions. We have added the information on medications in table 1 and have added a new analysis for the relative risk for preclinical hypertension, diabetes and hypertriglyceridemia and hypoalphalipoproteinemia in figure 3. We included medications as a covariate in our original models (as indicated in the figure legend), and medications are included in the definition of the risk groups for the new relative risk analysis (page 4).

“Preclinical hypertension was defined as blood pressure >130/85 mmHg or use of hypertensive medications. Preclinical hypertriglyceridemia was defined as triglyceride >1.7 mM or use of
lipid medications. Preclinical hypoalphalipoproteinemia was defined as HDL levels less than 1.0 mM in men or 1.3 mM in women or use of lipid medications. Prediabetes was defined as glucose >5.6 mM or use of diabetes medications.”

These new statistical analyses are now in the methods on page 5, last paragraph.

“The relative risk for prevalent preclinical risk factors for the obesity and fitness groups was assessed using main effects and interaction terms adjusting for age and sex using the method proposed by Zou [15]. When the interaction term was not significant, the model was re-run without the interaction term. When the interaction or obesity and/or fitness main effect was observed, a least squared difference post hoc was conducted to assess group differences.”