Author's response to reviews

Title: Weight change and incident metabolic syndrome in Iranian men and women; a 3 year follow-up study

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Author's response to reviews: see over
Dear Mr. Mark Todd
Assistant Editor of BMC-series journals

Thank you for considering our manuscript: "Weight change and incident metabolic syndrome in Iranian men and women; a 3 year follow-up study", Ms. Ref. NO. 1014196674217928; it has been revised based on reviewer comments and a point-by-point response to reviewers has been prepared.

We hope that this revised manuscript meets the reviewers’ approval and look forward to hearing from you.

Sincerely,
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Referee 1 (Vasilios G Athyros)

Comment

2. Agreed. The study was an observational study secondary to prospective analyses of the original data. This was added in limitation part. [Page 11, line 10]

3. Agreed. We addressed the issue in the limitation of the study. [Page 11, line 12-14]

Minor

Agreed. Corrected.
Referee 2 (Evangelos Liberopoulos)

1. Agreed. In our study about 43% of the eligible subjects were not included in the final sample analysis, because of lost to follow-up (n=2399), death (n=120) and missing data (n=112) [Page 4, line 2-6]. In comparison to the subjects who did not attend the follow-up visit, those who attended had higher values of age (44. vs. 40.8 years), BMI (27.3 vs. 26.5 kg/m²), WC (89.2 vs. 87 cm), systolic blood pressure (120.8 vs. 118.9 mmHg), diastolic blood pressure (78.6 vs. 77.5 mmHg), fasting plasma glucose (5.5 vs. 5.4 mmol/l), triglyceride (2.0 vs. 1.8 mmol/l), (all p values <0.05). However, there was no difference in HDL-C level between participants vs. nonparticipants [Page 6, lines 24, 25; page 7, lines 1, 2]. Therefore, the non participants were healthier in their baseline characteristic assessments; so, we may have overestimated the incidence of metabolic syndrome in the general population. We highlighted this issue in the result and limitation part. [Page 11, line 7-10]

2. Regarding the original NCEP ATPIII definition (Ref. 18) those who received antihypertensive medication and had blood pressure <130/80 mmHg were not defined as a component. Furthermore, we considered the antihypertensive medication as covariates in all of the analyses. Regarding AHA/NHLBI definition, we analyzed our data applying this definition; however, no change was found in the relative risks of MetS and its components using this definition. [Page 8, line 18-20]
3. Agreed. The paradox observed in our study regarding decreasing triglyceride and blood pressure despite the increasing incidence of MetS was addressed in major point 3 of referee 3 (Altan Onat).

Furthermore, we showed the prevalence of medication usage both at baseline and follow up in Table 1, however we did not have data regarding the details of lipid medication or using anti obesity drugs. As it is possible that using medication could affect the association of weight change and MetS components, we also performed analyses limited to subjects not treated for hypertension, dislipidemia or diabetes. Results were unchanged after excluding subjects treated with medications. [Page 8, line 15-17]

4. Agreed. Done. [page 9, line 1]

Minor comment

1. Agreed. Done.

2. Middle East Caucasian was explained in the abstract. [page 2, line 5]

3. The sentence was more clarified as “Therefore, it seems that investigations on the association of weight change and MetS are essential to clarify the relationship between weight change and mortality. “ [page 3, line 8]

4. Agreed. Many thanks to this especial comment. The relevant studies were included. (Ref. 11 and 12)
5. According to design of Tehran Lipid and Glucose Study, participants were examined at each phases (Ref. 17); so, in the current study, population were examined both at baseline (cross sectional or phase 1) and after a mean follow up of 3.1 years (phase 2). [page 4, lines 1, 5, 6]

6. Agreed. The issue was answered in minor comment 5.

7. Agreed. To examine the RR of developing MetS and its components, logistic regression models were fitted separately in subject who did not have MetS or its components at baseline, respectively [Page 6, lines 21, 22]. Hence, the normal subjects were those who were free of cited MetS component at baseline.

8. Agreed. We replaced “normally” instead of “symmetrically”. [page 7, line 14]

9. Agreed. The NCEP ATPIII threshold for defining MetS components were considered as high WC, high triglyceride, low HDL, high fasting plasma sugar and high blood pressure. [Page 5, line 18-22]

10. Agreed. Recent references were included in the manuscript. (Ref. 11, 12, 28, 29, 35-38, 40)

11. Regarding Table 3 and 4 : a) For assessing risk of development of each components of MetS according to weight change group, we included in our regression analyses only those subjects free of cited MetS component at baseline. [Foot note of Tables 3, 4; page 6, lines 21, 22] b) Agreed. Numbers of subjects were inserted.
1. Agreed. In our study, 1431 men and 2036 women with complete data on covariates were included in the analyses of tables 1-4, since there was no reason for excluding subjects with metabolic syndrome (MetS). When we aimed to assess the risk of weight change on incidence of each component; however, only subjects free of MetS component at baseline were included in the analyses (i.e. for calculating the risk of high waist circumference (WC), considering weight change groups, only subjects with normal WC at baseline were entered in the analysis [page 6, lines 21, 22, footnotes of table 3 and 4]. In Figure 1 incident cases of MetS in the course of the follow-up as dependent variable were tested in separate logistic regression analyses in which 394 men and 856 women of MetS at baseline were excluded, leaving 1037 men and 1180 women [legend Figure 1]. Regarding Table 1 (in revised manuscript), among men, we found 394 subjects with MetS at baseline and 484 MetS cases at the follow up; however from the latter, 274 subjects overlapped with baseline cases, with 210 new cases of MetS remained. Among women, we found 856 subjects with MetS at baseline and 969 MetS cases at the follow up, of which 699 subjects overlapped with baseline cases, hence 270 new cases of MetS remained. [page 7, line 14-19]
2  Agreed. In the regression analysis only those subjects free of cited MetS components at baseline were included (i.e. for calculating the risk of high WC, considering weight change groups, only subjects with normal WC at baseline were entered in the analysis). So the meaning of normal subjects was those who were free of the cited MetS component at baseline [page 6, lines 21, 22]. The total sample sizes for analyses highlighted in tables 2-4 were added to tables. Regarding Table 3 and, 4 those subjects who had the considered MetS component at the baseline were excluded, so the baseline values were not adjusted in the regression. [Foot note of Tables 3 and 4]

3  Agreed. Done.

Minor points

1. Agreed. Considering limitation in word count in the abstract, we reported the relative risks and 95% confidence interval only for all incident cases of MetS.

2. Agreed. Done. [page 4, line 8]

3. Agreed. Regarding physical activity, the issue was more clarified: Physical activity was categorized to three groups; vigorous, those who had hard physical activity (leisure time or occupational) at least three times a week; moderate, those who had hard physical activity at least once a week regularly; no, those without any regular hard physical activity. So, those with had hard physical activity at least three times a week was defined as vigorous. [page 4; line 15-18]

4. Agreed. Waist circumference was measured at umbilical level. [page 4, line 22]
5. Agreed. Done. [page 7, line 6]

6. Agreed. Done. [page 8, line 3]

7. Agreed. Done. [page 8, line 6]

8. Agreed. Done. [page 9, line 7]


10. Agreed. Done. [page 10, line 10]
Referee 3 (Altan Onat)

1. Agreed. Done. [page 4, line 4-6]

2. Agreed. The number of subjects in the five groups of weight changes was added to Tables 2-4 and page 6. Furthermore, based on the distribution of weight change in both genders, the weight change percent was divided into quintiles, which resulted to relatively similar number of subjects in each group. [page 6, line 3-7]

3. Agreed. Recently, in a non-diabetic population, we showed that despite an increasing trend in general and abdominal obesity, a favorable trend in total cholesterol in both genders and TG in men occurred, which was not related to the increasing usage of lipid lowering drugs. However, this trend was counterbalanced by unfavorable changes in HDL cholesterol, which was found to decrease in both genders especially in men (Ref. 15) [Page 9, line 24-26; page 10, lines 1, 2]. Furthermore, in a multi center study in different ethnic groups, using signal detection analysis, the best predictor of incident MetS was waist circumference (Ref. 27) [Page 9, lines 16, 17]. So, favorable trends in TG and BP were not enough to alleviate the risk of MetS in light of the increasing trend in general and central obesity. [Page 9, lines 22, 23]
4. Agreed. Considering the observational nature of our study, delineating the reason for this divergence between genders regarding weight gain and risk of abnormal glucose metabolism is difficult. However, in Turkish adults with a similar prevalence of MetS, women with normal glucose metabolism were more prone to incident diabetes than men (Ref. 36). Furthermore, in a recent population based study from Denmark, women who had gained and sustained considerable weight were more susceptible to development of new onset diabetes (Ref. 37). During the short term follow-up in our study, attained BMI (in phase 2) and BMI changes were more marked in women than men (mean of BMI change: 0.99 vs. 0.66 kg/m²; P<0.001, respectively). On the other hand, body weight is a stronger predictor of Type 2 diabetes than physical activity, considering the finding that physical activity was significantly lower in Iranian women than men (Ref. 38, 39). Hence, the higher prevalence of diabetes and abnormal glucose metabolism (i.e. impaired fasting glucose or impaired glucose tolerance) in Iranian women than in men was justifiable (Ref. 40). [page 10, line 12-23]

5. Agreed. Since the aim of this study was descriptive, we did not make large multivariate analyses; so it would have been difficult to interpret causality from our analyses. However, in The Insulin Resistance Atherosclerosis Study, using signal detection analysis, the best predictor of incident MetS was waist circumference (Ref. 27). Hence, regarding high prevalence of abdominal obesity in our females (Ref.28); the higher relative risk for incident MetS in Iranian females would be justifiable. [Page 9, line 16-19].

6. Agreed. Many thanks to this special comment. We cited three relevant studies (Ref. 20, 21, 36).
7. Agreed. In women we divided participants into those aged >50 years and ≤50 years; the analysis according to this classification highlighted that in women ≤50 years high BP component was not affected by weight gain. In those older than 50 years the relative risks of high WC and high BP considering weight gain groups were increased significantly. [Page 7, line 10-14; page 10, lines 25, 26; page 11, lines 1, 2]

Minor points

1. Agreed. Done.