Author's response to reviews

Title: Population attributable risk for diabetes associated with excess weight in Iranian adults: A population-based cohort study

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Author's response to reviews: see over
Dear Dr. Norton,

Greetings,

Thank you for considering our original manuscript entitled “Population attributable risk for diabetes associated with excess weight in Iranian adults” for peer review process. We also thank the two esteemed reviewers for their comprehensive review and scientific criticism and the comments given. The revised version of the manuscript according to the reviewers’ comments is submitted herewith. In addition, you may find the responses to the comments in detail below.

Looking forward to hearing from you at your earliest convenience.

Sincerely,

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Comments of Referee #1 and responses:

Referee #1: Even though the study is community-based study, follow-up ratio is too low [4728/(4122+4728) = 53.4%]. How do authors invite subjects to follow-up examinations? Are there any reasons for the low follow-up ratio?

Response: Since the beginning of TLGS in late 1997 (December), all the families (clusters) were invited to the study site using telephone and/or direct contact. After almost 3.6 years, the first follow-up study commenced and the subjects were invited according to the previous methods (telephone and/or direct contact). But, as a sizable proportion of people in the district 13 of Tehran are tenants (do not have their own home), the migration rate is high. This may be the main reason for the low follow-up ratio.

Referee #1: To check selection bias in 3.6-year follow-up examination, baseline characteristics should be compared between 4122 non-followed subjects and 4728 followed subjects.
Response: Agreed, the non-participants were relatively healthier in their baseline characteristics. In comparison to respondents, non-respondents had lower value of systolic blood pressure (119 vs. 117 mmHg), body mass index (26.9 vs. 26.2), waist circumference (88.2 vs. 86.5 cm), triglycerides (1.88 vs. 1.78 mmol/L), fasting plasma glucose (4.99 vs. 4.94 mmol/L), 2-h postchallenge plasma glucose (5.94 vs. 5.83 mmol/L). Therefore, we may have over estimated the incident diabetes in the general population. These points have been added to the method section and the limitation part of the discussion section.

Referee #1: Baseline prevalence of obesity in women is about twice of that in men (29.8% vs. 15.1%). On the other hand, incidence of DM is almost equal between sexes (73/1961 = 3.7% in men vs 109/2767 = 3.9% in women). These results indicate that effects of obesity on incident DM is considerably different among sexes. However, the authors have no attentions on sex-differences in their data analysis, and analyze the data together both sexes. First, baseline characteristics should be presented by sex. Subsequently, the follow-up data should be analyzed in each sex. When the results in men and in women are similar with each other, the two data sets can be combined.

Response: Agreed; the data reanalyzed. Except for diastolic blood pressure, the baseline characteristics of men and women were not identical statistically (Table below). In the logistic regression analyses, the crude and adjusted odds ratios for overweight/obesity were higher in women than in men; the sex-specific ORs have been added to the table 2 of the manuscript.

<table>
<thead>
<tr>
<th>Group Statistics</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>44.747</td>
<td>14.43</td>
<td>41.542</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>120.61</td>
<td>17.42</td>
<td>117.54</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>77.865</td>
<td>10.67</td>
<td>77.641</td>
</tr>
<tr>
<td>weight (Kg)</td>
<td>74.881</td>
<td>12.60</td>
<td>77.865</td>
</tr>
<tr>
<td>waist (cm)</td>
<td>89.009</td>
<td>10.97</td>
<td>87.592</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>25.999</td>
<td>3.964</td>
<td>27.687</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>91.018</td>
<td>9.748</td>
<td>89.326</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>205.95</td>
<td>41.70</td>
<td>212.84</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>180.34</td>
<td>114.9</td>
<td>156.58</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>38.341</td>
<td>9.093</td>
<td>45.181</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>132.53</td>
<td>35.65</td>
<td>136.06</td>
</tr>
</tbody>
</table>

There are some explanations for this finding. First, absolute weight gain in men were greater than women (2.27±4.9 vs. 1.92±4.9 Kg; P<0.05). The same pattern was observed in changes of waist circumference (5.6±5.3 vs. 3.4±7.5 cm, P<0.001). These changes among men may describe why the incidence of diabetes in men was almost similar to women despite higher proportion of obesity in women. Second, men were relatively older than women were (44.7±14.4 vs. 41.5±12.8 years, respectively; P<0.01); older age is a strong risk factor for incidence of diabetes. Finally yet importantly, the lost-to-follow-up rate was higher in women than in men. That is, some of the women who developed diabetes had been lost. However, in women, those with BMI < 25 kg/m2 had higher rates of loss to follow-up. These points have been added to the Discussion section.
Referee #1: The data set from 4728 followed subjects is 'paired' data; baseline and 3.6-year follow-up in all the subjects, and output (dependent variable) is dichotomous. Logistic regression analysis should be used for the data to estimate odds ratio and its 95% CI.

Response: Agreed; in the section of statistical analysis, the term “general linear models” has been changed to the term “logistic regression models”. However, the “general linear model (GLM)” incorporates a number of different statistical models including linear regression models, Cox regression models, and logistic regression models. Indeed, logistic regression model is a GLM.

Referee #1: Anthropometric 3.6 year-changes (Table 2) in 182 subjects with incident DM may be just changes with aging. The changes in the 182 subjects should be compared with those in the other subjects without incident DM.

Response: Agreed, the table 2 has been deleted since it was not informative because of the “aging”.

Referee #1: Does ‘linear-by-linear chi2-test’ mean Mantel-Haenzel chi2-test?

Response: No. Linear-by-linear chi2-test is in fact the “chi2-for-trend.” The Linear-by-linear chi2-test in SPSS is equal to Chi2-for-trend. This method tests the significance of trend of proportions across levels of an ordinal variable (in this case BMI groups).

Referee #1: The 3.6-year follow-up is not enough to show reliable results in prospective studies. The TLGS study has been setup in 1997, and follow-up interval is 3.6 year. So, the study may finish 2nd follow-up examination by now. The authors are possible to include the 2nd follow-up results.

Response: Agreed, the 2nd follow-up survey is underway and will be completed several months later. In fact, the study began in 1997 and the cross-sectional phase completed in 2000; the first follow-up survey began in 2001 and completed in 2004 and the second follow-up survey began in 2005 and will be completed in 2008.

Referee #1: Trends in prevalence of obesity/overweight in Iranian general population should be cited (Examples: National Survey for health/nutrition). Has the prevalence in Iran been increasing or decreasing?

Response: The increasing prevalences of overweight and obesity in an urban Iranian population have been published previously. (Ref. No.2)

Referee #1: The study subjects are selected from Tehran’s urban population. Does the prevalence of obesity/overweight in the area indicate the prevalence in Iranian general population? To discuss attributable risk by obesity/overweight in Iran, the prevalence in Iranian general population should be used in the estimation of population attributable risk.

Response: Yes, the participants of TLGS are a representative sample of an urban Iranian population. The detailed information is available in “CVD Prevention” journal (Ref. No. 18). Therefore, the prevalence of obesity/overweight estimated in this study would indicate its
prevalence in an Iranian “urban” population; however, the results may not be extrapolated to the “rural” population. (The rationale and design of TLGS is available upon request)

Referee #1: To discuss attributable risk by obesity/overweight in Iran, the prevalence in Iranian general population should be used in the estimation of population attributable risk.

Response: Agreed; we changed the “Iranian” to the “Tehranian” in the abstract, title, and the discussion section; however, again, it should be mentioned that participants of TLGS are a representative sample of Iranian urban population.

Referee #1: The data according to BMI-subgroups (Table 4) may not be essential for authors’ aims.

Response: Agreed, the table has been deleted.

Comments of Referee #2:

Referee #2: The authors should provide more and clear information on the exact period of screening and data collection (eg, the questionnaire) regarding both surveys: at baseline and follow-up.

Response: Agreed, further information has been added to the method section.

Referee #2: Also, the participation rates and the proportion of subjects that was submitted to the glucose tolerance test during the follow-up phase should be referred.

Response: Participation rate was about 61% in the total cohort and 53.4% in the sample studied here. OGTT was performed for all the subjects aged >18 years. Therefore, in the present study, all subjects had 2h-PG both in the cross-sectional and follow-up phases.

Referee #2: In the statistical analyses section, it is not clear to me if for the calculation of ORs the logistic regression analysis or another test was used.

Response: General linear model (GLM) has been changed to the logistic regression model. (Logistic model is a subtype of GLM)

Referee #2: Additionally, in the same section, the statement “Population attributable risks were calculated with the use of formula \( \frac{P(OR-1)}{[P(OR-1)+1]} \times 100 \), where …” should accompanied with the respective reference.

Response: Agreed, the reference No. 23 added.
Referee #2: In the first category of the limitations should be included the lack of data regarding the socio-economic status and the dietary habits of the population.

Response: agreed, the lack of socio-economic and dietary habit data added.

Referee #2: page 3, paragraph 2, the sentence of line 8 is uncompleted.

Response: Agreed, corrected.

Referee #2: page 5, first paragraph, “… with known or newly diagnosed type 2 diabetes ” should be corrected to “… those with known or newly diagnosed type 2 diabetes …, those with missed …”

Response: Agreed, corrected.

Referee #2: title of table 2, “Wight …” to “Weight …”

Response: Agreed, corrected.

Referee #2: The present study shows that the prevalence of obesity is significantly higher among women than in men. Accordingly, it would be of interest to calculate ORs and estimated PAR for diabetes -contributed to overweight/obesity- separately among women and men; the derived results should to be presented in another table. In that manner, the comparison with other studies (eg, Hu FB et al, N Engl J Med 2001;345:790-7) would be facilitated and, simultaneously, the authors have the opportunity to discuss about the possible differences on the contribution of obesity in developing diabetes in both sexes

Response: Agreed, table 2 now presents the data of total as well as sex-specific results.