PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Sex differences in body anthropometry and composition in individuals with and without diabetes in the UK Biobank
AUTHORS	Peters, Sanne; Huxley, Rachel; Woodward, Mark

VERSION 1 - REVIEW

REVIEWER	Tim Frayling University of Exeter, UK
REVIEW RETURNED	06-Oct-2015

GENERAL COMMENTS	This paper provides a large descriptive analysis of body weight and measurement between people with and without the two main types of diabetes and further broken down by sex. The starting point is all people in the UK Biobank (therefore aged 40-70) after excluding those reporting cardio vascular disease. The strength of the study is that it is a single very large study that is largely unbiased by disease ascertainment. The study therefore provides a largely unbiased look at the differences in BMI, Waist hip ratio etc between men and women with and without the two types of diabetes. I have the following comments and suggestions 1. The results provide estimates of the differences in body size between men and women with and without diabetes that are largely free from ascertainment biases. These estimates are however not free from reporting biases. The authors note many of the caveats but I am still concerned that even a small proportion of type 2 diabetic individuals in the group classified as type 1 would distort the BMI and WHR estimates. The fact that 17% and 19% of women and men classified as type 1 diabetic are taking non insulin hypoglycaemic medication makes me concerned that some are type 2. And because the differences in BMI between type 2 diabetic individuals and non diabetic individuals are so large, it would not take much missclassification for the type 1 BMI estimates to be biased upwards. Another explanation of the results is that insulin therapy can cause weight gain but to help distinguish between these possibilities the authors could check how many of the people they've classified as type 1 were not on insulin in the first year since diagnosis – and recalculate the frequency of non insulin therapies, BMI etc . As it stands, these uncertainties mean the main message of the paper is that women with type 2 diabetes are more overweight than men with type 2 diabetes. The authors speculate, quite reasonably, that this could explain the excess cardio vascular risk in female diabetic individuals, although the data don't allow them to prove this as they point out in the caveats. The authors also speculate, again quite reasonably , that women "need" to be more overweight to develop type 2 diabetes and CVD because they have larger or more efficient adipose storage capacity. 2. There is no mention of how the authors accounted for the different ethnicities within the biobank. Although small as a proportion there are still sufficiently large numbers of people of South Asian ancestry

	for example that could confound any quantification of BMI vs diabetes (because diabetes occurs in South Asians at much lower BMIs) 3. The authors should show some plots of the distribution of ages of diagnosis. From our look at the data there are some people who have confused age at diagnosis with time since diagnosis. This is another source of misclassification between type 1 and type 2. We have defined type 2 as not requiring insulin in the first year since diagnosis and being more than 35 years of age at diagnosis.

REVIEWER	Kristine Færch, MSc PhD Steno Diabetes Center, Gentofte, Denmark
REVIEW RETURNED	11-Oct-2015

GENERAL COMMENTS	This study from the UK Biobank shows that differences in body size between individuals with and without type 2 diabetes are larger for women than for men. In contrast, no sex differences are seen in body size differences between individuals with and without type 1 diabetes. The authors suggest that the findings may partly explain why women with type 2 diabetes have higher relative risk of CVD than men. The study is interesting and novel and based on a large number of individuals (~500.000). The manuscript is well-written and the analyses are performed in a proper way. Major comments: 1. The authors want to examine if sex differences in body size can explain the higher relative CVD risk in women compared with men with diabetes. Information on CVD was available from the participants but not used in the study. Why were individuals with CVD excluded from the study? In order to answer the research question more precisely, these data could have been used. Including these data would also make the conclusion much stronger and not so speculative. 2. Diagnosis of diabetes was based on self-report. In general, women tend to seek a doctor more frequent than men, which is likely to result in a larger proportion of women being diagnosed with diabetes than men. How will this affect the results? Minor comments: 1. The numbers presented in Figure 1 are exactly the same as those presented in Table 2 (two columns to the right). Therefore, they could be omitted from the table without losing any information. Alternatively, the body size variables in Figure 1 could be standardised to allow direct comparison of the differences (in SD units). 2. The results from the subgroup analysis (Table 3) could be presented in a figure instead (same type as Figure 1). That would make the results more reader-friendly and ease the interpretation.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Tim Frayling
Institution and Country: University of Exeter, UK
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below This paper provides a large descriptive analysis of body weight and measurement between people with and without the two main types of diabetes and further broken down by sex. The starting point is all people in the UK Biobank (therefore aged 40-70) after excluding those reporting cardio vascular disease. The strength of the study is that it is a single very large study that is largely unbiased by disease ascertainment. The study therefore provides a largely unbiased look at the differences in BMI, Waist hip ratio etc between men and women with and without the two types of diabetes. I have the following comments and suggestions
1. The results provide estimates of the differences in body size between men and women with and without diabetes that are largely free from ascertainment biases. These estimates are however not free from reporting biases. The authors note many of the caveats but I am still concerned that even a small proportion of type 2 diabetic individuals in the group classified as type 1 would distort the BMI and WHR estimates. The fact that 17% and 19% of women and men classified as type 1 diabetic are taking non insulin hypoglycaemic medication makes me concerned that some are type 2. And because the differences in BMI between type 2 diabetic individuals and non diabetic individuals are so large, it would not take much misclassification for the type 1 BMI estimates to be biased upwards. Another explanation of the results is that insulin therapy can cause weight gain but to help distinguish between these possibilities the authors could check how many of the people they've classified as type 1 were not on insulin in the first year since diagnosis – and recalculate the frequency of non insulin therapies, BMI etc . As it stands, these uncertainties mean the main message of the paper is that women with type 2 diabetes are more overweight than men with type 2 diabetes. The authors speculate, quite reasonably, that this could explain the excess cardio vascular risk in female diabetic individuals, although the data don't allow them to prove this as they point out in the caveats. The authors also speculate, again quite reasonably , that women "need" to be more overweight to develop type 2 diabetes and CVD because they have larger or more efficient adipose storage capacity.

We agree with the reviewer that the classification of individuals into type I and type II diabetes is arbitrary, and prone to misclassification. Some of the individuals classified as type I could have developed features of type II diabetes, which could explain the use of oral hypoglycaemic medication in some individuals. As per this reviewer's third suggestion (below), we conducted a sensitivity analysis in which we classified type I diabetes as those individuals aged <35 at diagnosis who reported using insulin but no other diabetes treatment. The results from this analysis are virtually identical to our main findings, and are shown in eTable 1.

2. There is no mention of how the authors accounted for the different ethnicities within the biobank. Although small as a proportion there are still sufficiently large numbers of people of South Asian ancestry for example that could confound any quantification of BMI vs diabetes (because diabetes occurs in South Asians at much lower BMIs)

Thank you for this suggestion. We have added information on ethnic background to Table 1, and have conducted a subgroup analysis comparing individuals with a white background compared to those with a mixed or non-white background. These analyses didn't provide evidence for a substantial impact of ancestry on the observed sex differences. The results are now added to Table 3 and Figure 2.

3. The authors should show some plots of the distribution of ages of diagnosis. From our look at the data there are some people who have confused age at diagnosis with time since diagnosis. This is another source of misclassification between type 1 and type 2. We have defined type 2 as not requiring insulin in the first year since diagnosis and being more than 35 years of age at diagnosis.

We agree that some individuals could have confused age at diagnosis with time since diagnosis. UK Biobank participants with a self-reported history of diabetes were only asked at what age they were diagnosed; from this we derived time since diagnosis (i.e. separate questions on age at diagnosis and

time since diagnosis were not asked). Our new eFigure 1 shows the distribution of self-reported age at diagnosis, separately for individuals classified as type I and type II diabetes, following the definitions in our main analyses. Information on time to first initiation of insulin is not available in the UK Biobank, and we were therefore unable to use such information in our classification of diabetes subtypes.

Reviewer: 2
Reviewer Name: Kristine Færch, MSc PhD
Institution and Country: Steno Diabetes Center, Gentofte, Denmark
Please state any competing interests or state 'None declared': None declared

This study from the UK Biobank shows that differences in body size between individuals with and without type 2 diabetes are larger for women than for men. In contrast, no sex differences are seen in body size differences between individuals with and without type 1 diabetes. The authors suggest that the findings may partly explain why women with type 2 diabetes have higher relative risk of CVD than men. The study is interesting and novel and based on a large number of individuals (~500.000). The manuscript is well-written and the analyses are performed in a proper way.

Major comments:
1. The authors want to examine if sex differences in body size can explain the higher relative CVD risk in women compared with men with diabetes. Information on CVD was available from the participants but not used in the study. Why were individuals with CVD excluded from the study? In order to answer the research question more precisely, these data could have been used. Including these data would also make the conclusion much stronger and not so speculative.

We excluded individuals with prior CVD from our main analyses because we aimed to determine whether a sex difference in body composition associated with diabetes could explain the findings from our previous meta-analyses using cohort studies, in which we showed that women with diabetes are at a considerably greater excess risk for future CHD and stroke as compared to men. To avoid the issue of reverse causality, the evidence in support, or against, our findings is clearer when analysing people without pre-existing CVD. We have explained this in the methods section of the revised manuscript. However, we agree with the referee that it is also interesting to see how body size and diabetes status are associated in a general population. Repeating our analyses on all individuals, including those with prior CVD yielded very similar findings. The results are provided in our new eTable 2.

2. Diagnosis of diabetes was based on self-report. In general, women tend to seek a doctor more frequent than men, which is likely to result in a larger proportion of women being diagnosed with diabetes than men. How will this affect the results?

We agree with the reviewer that differences between men and women in consultation behaviour might lead to a sex differential in the likelihood of being diagnosed with diabetes. If, as the reviewer suggests, a larger proportion of women than men would be diagnosed with diabetes (i.e. relative overdiagnosis in women), it might be that the change in body size associated with diabetes in women would have been smaller than that in men, as a result of more frequent consultations in women. If this is the case, our results are most likely to be an underestimate of the true sex differences in differences in body size associated with diabetes. It is however important to note that results from the population-based diabetes register in Scotland do not support this hypothesis. These Scottish data showed that mean BMI close to the date of diagnosis of type 2 diabetes mellitus was about 2 kg/m2 higher in women as compared to men, which is in line with the current findings. The Scottish study

also showed that HbA1c levels within 1 year of diagnoses were broadly similar in men and women, indicating that men and women were diagnosed at a similar stage of disease.

In the discussion section, we now state that:

'The Scottish data showed that the difference in BMI at diagnosis with diabetes was unrelated to the levels of HbA1c levels within 1 year of diagnoses. These data indicate that men and women were diagnosed at a similar stage of disease, despite the higher consultation rates in women in the general population'

Minor comments:
1. The numbers presented in Figure 1 are exactly the same as those presented in Table 2 (two columns to the right). Therefore, they could be omitted from the table without losing any information. Alternatively, the body size variables in Figure 1 could be standardised to allow direct comparison of the differences (in SD units).

We agree that Table 2 and Figure 1 provided some duplicate information; we therefore have removed the last two columns.

2. The results from the subgroup analysis (Table 3) could be presented in a figure instead (same type as Figure 1). That would make the results more reader-friendly and ease the interpretation.

Thank you for this suggestion. We have presented the comparisons for type II diabetes in Figure 2. Since there was little evidence for sex differences for type I diabetes, and precision was lower, table 3 shows the results for subgroup analyses for type I.

VERSION 2 – REVIEW

REVIEWER	Tim Frayling University of Exeter UK
REVIEW RETURNED	26-Oct-2015

GENERAL COMMENTS	I have the following outstanding comments: 1. There are still some oddities in the analyses of type 1 diabetes: a. The stricter definition of type 1 diabetes would be to take those diagnosed less than 35 years, and required insulin within one year of diagnosis (not simply exclusive use of insulin which is possible in a classic type 2 patient after many years of diabetes). See the “Started insulin within one year diagnosis of diabetes” variable. b. The results from Etable 1, using <35 years at age diagnosis in the type 1 defintion are not “virtually identical” to the primary results shown in main table 2. The table shows that, when using the age 35 years cut off, the individuals with type 1 diabetes are not any different in BMI or body fat percentage. eTable2 then shows that individuals with type 1 do have higher BMIs (but again not higher fat %) when adding back in those with vascular disease. This is all very confusing and casts the general conclusions about type 1 diabetes in doubt. There are also some confusing headings in this table with “type I” mixed up with “type II” in several places. 2. I think the authors should tone down the inference that their results provide major insight into the link between female diabetes and CVD. They have not proven anything about CVD, just infer that

	the link could be due to greater differences in BMI and fat percentage. For example the sub headings in the discussion and the conclusion in the abstract “Sex differences in body size associated with diabetes might underpin some of the excess risk for CVD in women with type II diabetes.” Well true but lots of things “might underpin” some of this association. The data hasn’t shown this. Likewise “The role of body size in explaining sex differences in the risk of CVD in type II diabetes” as a sub heading is a little misleading. 3. Thanks for including efigure1 but the slight incline in “type 2 diabetes” diagnosed in childhood suggests that some people have confused year at diagnosis with year since diagnosis. Again it is worth performing sensitivity analyses with a stricter definition of type 2 diabetes – exclude those saying diagnosis less than 35 and those that used insulin within the first year.

REVIEWER	Kristine Færch Steno Diabetes Center, Gentofte, Denmark
REVIEW RETURNED	27-Oct-2015

GENERAL COMMENTS	The authors have addressed all my comments and concerns.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Tim Frayling
Institution and Country: University of Exeter, UK
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
I have the following outstanding comments:
1. There are still some oddities in the analyses of type 1 diabetes:
a. The stricter definition of type 1 diabetes would be to take those diagnosed less than 35 years, and required insulin within one year of diagnosis (not simply exclusive use of insulin which is possible in a classic type 2 patient after many years of diabetes). See the “Started insulin within one year diagnosis of diabetes” variable.
Thank you. We have added analyses using the suggested definition. The results are displayed in eTable 2.

b. The results from eTable 1, using <35 years at age diagnosis in the type 1 definition are not “virtually identical” to the primary results shown in main table 2. The table shows that, when using the age 35 years cut off, the individuals with type 1 diabetes are not any different in BMI or body fat percentage. eTable2 then shows that individuals with type 1 do have higher BMIs (but again not higher fat %) when adding back in those with vascular disease. This is all very confusing and casts the general conclusions about type 1 diabetes in doubt. There are also some confusing headings in this table with “type I” mixed up with “type II” in several places.

Thanks for spotting the typos in the eTables' headings, these have now been resolved. Thanks also for commenting on the results for Type I diabetes. The number of individuals classified as Type I diabetes is relatively small and it is therefore inevitable that minor variation occurs in using different definitions. This primarily has affected the within-sex comparisons (i.e. the comparison of men and women with and without diabetes), but is less likely to have affected the between sex comparisons.

In the limitations section we therefore state that:

'The identification of individuals with diabetes, and the classification into type I or type II diabetes, was based on self-reported data, and misclassification of diabetes status will have occurred. However, any misclassification will have been similar in women and men and thus the between sex comparisons remain valid.'

It is important to emphasise that our main findings remain similar regardless of the definition of type I and type II diabetes used, that is, the differences in body size associated with diabetes are considerably greater in women than in men in type II diabetes, but not in type I diabetes.

2. I think the authors should tone down the inference that their results provide major insight into the link between female diabetes and CVD. They have not proven anything about CVD, just infer that the link could be due to greater differences in BMI and fat percentage. For example the sub headings in the discussion and the conclusion in the abstract “Sex differences in body size associated with diabetes might underpin some of the excess risk for CVD in women with type II diabetes.” Well true but lots of things “might underpin” some of this association. The data hasn’t shown this. Likewise “The role of body size in explaining sex differences in the risk of CVD in type II diabetes” as a sub heading is a little misleading.

We agree with the reviewer and have revised the manuscript accordingly. We have removed the subheadings. The revised abstract conclusion is:

'Differences in body size associated with diabetes were significantly greater in women than in men in type II diabetes but not in type I diabetes. Prospective studies can determine whether sex differences in body size associated with diabetes underpin some of the excess risk for CVD in women with type II diabetes.'

The revised conclusion is:

'In conclusion, differences in body size associated with diabetes were significantly greater in women than in men in type II diabetes but not in type I diabetes. A greater difference in body anthropometry associated with diabetes in women compared with men might be responsible for the greater excess risk for cardiovascular disease in women with type II diabetes as compared to men. Sex differences in the effect of type I diabetes and vascular events, however, are likely to be driven by mechanisms other than body anthropometry. These hypotheses can be explored in the UK Biobank, once sufficient numbers of events have accrued. In either case, adequate weight control remains crucial for the prevention or delay of diabetes, and for the onset of its major vascular complications.'

3. Thanks for including efigure1 but the slight incline in “type 2 diabetes” diagnosed in childhood suggests that some people have confused year at diagnosis with year since diagnosis. Again it is worth performing sensitivity analyses with a stricter definition of type 2 diabetes – exclude those saying diagnosis less than 35 and those that used insulin within the first year.

As per our response to comment 1a, we have redone our analyses following the suggested definition. As well as creating the new eTable 2, we have also added two panels to eFigure 1. The two bottom panels show the distribution of participants by age at diagnosis using the stricter definition of type II diabetes. ‘That is, type I diabetes was defined as an age at diagnosis <35 years, and having started insulin within one year of diagnosis of diabetes. All other participants with a self-reported history of diabetes were classified as Type II diabetes.’

Reviewer: 2

Reviewer Name: Kristine Færch
Institution and Country: Steno Diabetes Center, Gentofte, Denmark
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors have addressed all my comments and concerns.
Thank you.

VERSION 3 - REVIEW

REVIEWER	Tim Frayling Exeter University
REVIEW RETURNED	02-Dec-2015

GENERAL COMMENTS	R2 I am sorry if this sounds overly pedantic, I realise this point doesn't affect the main conclusion of the paper which is about type 2 diabetes, but the abstract strongly implies that there IS a difference in BMI in people with T1D versus non diabetic individuals. e.g. "Body size was consistently higher in individuals with diabetes than in individuals without diabetes, especially type II diabetes." This implies type 1 as well , just not as strong. I have put the BMI data from the three definitions of type 1 diabetes into the same table below. Paying careful attention to the 95% CIs and effect sizes, as the definition of T1D becomes stricter, the effect of BMI becomes weaker and not significant at p <0.05. The male and female effects start to trend in the opposite direction meaning the combined effects will partially cancel out. Indeed the combined effect in figure 1 is 0.26 (-0.39, 0.91) – not significant. Otherwise I am happy the authors have answered the queries. BMI effects Diff women T1D vs non T1D Diff men T1D vs non T1D 0.93 (0.41, 1.45) 0.62 (0.24, 1.00) Diag <30yrs + insulin Table 2 0.21 (-0.31, 0.73) -0.04 (-0.41, 0.34) Diag <35yrs + insulin only Etable 1 0.24 (-0.20, 0.68) -0.19 (-0.51, 0.13) Diag <35yrs + insulin in 1st yr Etable 2

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Tim Frayling
Institution and Country
Exeter University
Please state any competing interests or state 'None declared':
None
Please leave your comments for the authors below
R2

I am sorry if this sounds overly pedantic, I realise this point doesn't affect the main conclusion of the

paper which is about type 2 diabetes, but the abstract strongly implies that there IS a difference in BMI in people with T1D versus non diabetic individuals. e.g. “Body size was consistently higher in individuals with diabetes than in individuals without diabetes, especially type II diabetes.” This implies type 1 as well , just not as strong. I have put the BMI data from the three definitions of type 1 diabetes into the same table below. Paying careful attention to the 95% CIs and effect sizes, as the definition of T1D becomes stricter, the effect of BMI becomes weaker and not significant at p <0.05. The male and female effects start to trend in the opposite direction meaning the combined effects will partially cancel out. Indeed the combined effect in figure 1 is 0.26 (-0.39, 0.91) – not significant. Otherwise I am happy the authors have answered the queries.

BMI effects

Diff women T1D vs non T1D Diff men T1D vs non T1D

0.93 (0.41, 1.45) 0.62 (0.24, 1.00) Diag <30yrs + insulin Table 2

0.21 (-0.31, 0.73) -0.04 (-0.41, 0.34) Diag <35yrs + insulin only Etable 1

0.24 (-0.20, 0.68) -0.19 (-0.51, 0.13) Diag <35yrs + insulin in 1st yr Etable 2

Thank you. We agree with this comment and have revised the abstract accordingly. The revised sentence is:

'Body size was higher in individuals with diabetes than in individuals without diabetes, particularly in type II diabetes.'