PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between body mass index and obesity-related cancer risk in men and women with type 2 diabetes in primary care in the Netherlands: a cohort study (ZODIAC-56)
AUTHORS	Hendriks, Steven; Schrijnders, Dennis; Hateren, Hans; Groenier, Klaas; Siesling, Sabine; Maas, Angela; Landman, Gijs; Bilo, Henk; Kleefstra, N.

VERSION 1 – REVIEW

REVIEWER	Sanne Peters University of Oxford, UK
REVIEW RETURNED	08-Aug-2017

GENERAL COMMENTS	The Paper by Hendriks and colleagues set out to evaluate the association between BMI and obesity-related cancers in a large cohort of patients with type 2 diabetes in the Netherlands. The authors found that a 5kg/m2 increase in BMI was associated with a 12% higher risk of obesity-related cancer in men and with a 15% higher risk of obesity-related cancer in women. BMI was associated with non-sex-specific obesity-related cancers in men but not women. BMI was associated with sex-specific obesity-related cancers in women but not men. The study is of interest and the topic is worth investigating. However, the manuscript could be improved if some issues would be considered and/or clarified. 1. In the discussion section, the authors conclude that 'Important differences between men and women were found'. This conclusion is not supported by the findings of the study, even though the authors state that 'it is unclear whether there is a sex difference in the association between BMI and obesity-related cancers in patients with type 2 diabetes'. The authors should add formal tests for interaction to quantify and examine these possible sex differences. 2. In the discussion section, the authors state that 'results concerning the sex-specific cancers showed the opposite'. Can sex-specific cancers be compared considering that prostate cancer and female-specific cancers are very different conditions, with a different aetiology. Some rewording is needed. 3. Table 2-4. The authors present the HRs for the covariables in the models without discussing them further. It may not be needed to present them.

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	Instead, it may be more meaningful to conduct subgroup analyses by these variables to determine whether the sex-specific association between BMI and cancers differs across these subgroups. This would be relevant for all confounders and age, but particularly for diabetes duration which attenuated the relationship between BMI and colon cancer in a previous study (reference 7). Stratification by HbA1c levels also seems especially relevant in this population. 4. Further specification on the definition of the outcomes in the methods and table legends would be useful. At present, no ICD-codes are provided. 5. The authors state that insufficient events had occurred to examine site-specific cancers. Can the authors specify the number of incident cases for each of the individual site-specific cancers? 6. It would be useful if the authors could add some discussion on the grouping of obesity-related cancers. How robust and certain are these relationships and could other cancers be considered. In fact, it may be worth to conduct an analysis on all cancers to see whether there is indeed no association. 7. The duration of follow-up is mentioned for non-sex-specific cancers, but not for the whole study. Can these be added to the abstract and results? Related to that, was there any loss to follow-up? 8. It would be helpful to add the total number of incident cases within BMI categories to table 5. 9. It is not very clear how the multiple imputation was conducted. Which variables were included in the imputation model and what package or procedure was used? 10. Table 1: How was smoking defined? Did this include previous smokers? 11. Table 1: A considerable proportion of patients was not on diabetes medication. This should be clarified. Does this mean that they were all on dietary interventions? 12. Tables: The units of measurement should be added for each covariable. 13. Which adjustments were made in Table 5?

REVIEWER	Dr. Isaac Aladeniyi University of Ibadan, Ibadan, Oyo state, Nigeria.
REVIEW RETURNED	18-Aug-2017

GENERAL COMMENTS	Great work but some unclear issues were observed, more in the methods. 1. With regards to the study design,there appear to be no reference group in this study for ease comparison of the risk. We may ask, could this risks as enumerated in this study be same among type 1 D.M patients or perhaps with the general population? 2. The method of patient selections were also not clearly enumerated. It may be interesting to know, if other risk factors that

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	are possible confounders for some of the cancers of interest in the patients selected were considered and how they were addressed, particularly in the analysis. 3. The method of diagnosis of the patients in the study should be mentioned, particularly, for the cancer cases, were they all autopsies or clinical conclusions by physicians? 4. Data collected for this study may need to be mentioned because the paper only mentioned data collected by ZODIAC and NKR. 5.In categorising BMI in line 6 under statistical analysis, the demarcation between the groups overlapped, this may create a problem of misclassification of patients and thus affect analysis. 6. I suppose that your conclusion is rather too emphatic and ambitious, given the fact of your claim as the first to conduct this study on the a large scale and your study design. I suggest you tone down a little. Further studies with advanced method may support your findings in future. 7. I suggest the author should review the methods, it's a good study worthy of publication.

REVIEWER	Gisele M Carriere, Senior Social Science Researcher Statistics Canada, Health Analysis Division Canada
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	Thank you for the opportunity to review your research. These results are an important contribution to this area of epidemiology since your results demonstrate the complexity of interaction of patient sex and type of cancer in the relation of BMI to obesity-related cancer incidence. I have the following comments: 1) Others previously and yourselves have also indicated that BMI and type 2 diabetes may confound associations to cancer incidence. Although you state that more specific obesity-related cancer sites (within all obesity-related cancers) were too small to analyse, your discussion on page 13 regarding sex differences in the association of BMUI and non sex-specific obesity-related cancers had me wondering about results for gastrointestinal cancers (or at least gastric-cardia). If that number were reportable, and sex differences remained, it would further support sex-differences for adiposity as plausible explanation. 2) How many cases from the ZODIAC -project did NOT link to the cancer registry? It would be good to report the number of linked cases as a percentage of the cases included for study after linkage. 3) Small edit required on page 9, second paragraph, second line:" .... with a non-obesity-related cancer before during follow-up." Was it "before" or 'during" ? Great work.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sanne Peters
Institution and Country: University of Oxford, UK
Please state any competing interests: None declared

The Paper by Hendriks and colleagues set out to evaluate the association between BMI and obesity-related cancers in a large cohort of patients with type 2 diabetes in the Netherlands. The authors

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found that a 5kg/m2 increase in BMI was associated with a 12% higher risk of obesity-related cancer in men and with a 15% higher risk of obesity-related cancer in women. BMI was associated with non-sex-specific obesity-related cancers in men but not women. BMI was associated with sex-specific obesity-related cancers in women but not men.

The study is of interest and the topic is worth investigating. However, the manuscript could be improved if some issues would be considered and/or clarified.

1. In the discussion section, the authors conclude that 'Important differences between men and women were found'. This conclusion is not supported by the findings of the study, even though the authors state that 'it is unclear whether there is a sex difference in the association between BMI and obesity-related cancers in patients with type 2 diabetes'. The authors should add formal tests for interaction to quantify and examine these possible sex differences.

Response: First of all, we would like to thank the reviewer for her valuable comments.

Because the outcome measure differs between sexes (prostate cancer in men, and ovarian, endometrial and breast cancer in women), it is impossible to compute a formal test for the interaction between sex and BMI in the analysis of the total group of obesity-related cancers (sex-specific and non sex-specific combined).
It is only possible to investigate the interaction between sex and BMI in the analysis for non sex-specific obesity related cancers, however we have explicitly chosen not to do this. When adding an interaction term to the model, one assumes that the effect of the other covariates (i.e. confounders) is the same in men and women. However, this does not have to be the case at all. Therefore we have chosen to conduct stratified analyses for men and women.

The conclusion is in our opinion supported by the findings of our study. We believe that it is allowed to conclude that there are sex differences when a relation is found in only one of the sexes, without formal testing for interaction, of course, with some reservations as mentioned.

2. In the discussion section, the authors state that 'results concerning the sex-specific cancers showed the opposite'. Can sex-specific cancers be compared considering that prostate cancer and female-specific cancers are very different conditions, with a different aetiology. Some rewording is needed.

Response: We agree with the reviewer that it is not possible to directly compare sex-specific cancers. We have changed this section of the discussion into the following:
"Results concerning the sex-specific cancers showed that BMI was associated with ovarian, endometrial and postmenopausal breast cancer in women. No association between BMI and advanced prostate cancer was found in men."

3. Table 2-4. The authors present the HRs for the covariables in the models without discussing them further. It may not be needed to present them. Instead, it may be more meaningful to conduct subgroup analyses by these variables to determine whether the sex-specific association between BMI and cancers differs across these subgroups. This would be relevant for all confounders and age, but particularly for diabetes duration which attenuated the relationship between BMI and colon cancer in a previous study (reference 7). Stratification by HbA1c levels also seems especially relevant in this population.

Response: We have chosen to present the covariables in the models to make the data as insightful as possible.

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We thank the reviewer for the idea to perform subgroup analyses, however we believe it is better not to perform these analyses. We followed the advice of Assmann et al. (Subgroup analysis and other (mis)uses of baseline data in clinical trials. THE LANCET • Vol 355 • March 25, 2000) not to undertake subgroup analyses on an ad hoc basis, because this would amount to a 'fishing expedition'.

In the introduction, we indeed wrote that diabetes duration attenuated the relationship between BMI and colon cancer in a previous study. However, we have wrongly described this study. Reference 7 described that an increased risk for obesity-related cancers was observed for patients who suffered from obesity for a total duration of 4 years or more. It was impossible for us to conduct a subgroup analysis stratified to obesity duration as we do not have this data available.

We have changed the introduction into the following:
"Another study investigated this association with colon cancer and found only a significant relationship in patients who suffered from obesity for a total duration of 4 years or more."

4. Further specification on the definition of the outcomes in the methods and table legends would be useful. At present, no ICD-codes are provided.

Response: We thank the reviewer for this suggestion. We have now added the ICD-codes to the methods section and to the table legends. Furthermore we have added that all included cancer cases were confirmed histologically by a pathologist, to the main text.

We have added the following:
"The non sex-specific cancer group consisted of gastric-cardia (ICD C16.0), colorectal (ICD C18,19,20), liver (ICD C22), gall bladder (ICD C23), pancreas (ICD C25) and kidney cancer (ICD C64) and adenocarcinoma of the esophagus (ICD C15.5 + morphological codes 8140 or 8560). In men, the sex-specific cancer group was formed by advanced prostate cancers only (C61 + TNM 3 or 4 or GLEASON > 7) (further referred to as prostate cancer). In women, the sex-specific cancer group consisted of ovarian (ICD C56), endometrial (ICD C54.1) and postmenopausal breast cancer (ICD C50) (further referred to as ovarian, endometrial and breast cancer)."

And

"All included cancer cases were histologically confirmed by a pathologist."

5. The authors state that insufficient events had occurred to examine site-specific cancers. Can the authors specify the number of incident cases for each of the individual site-specific cancers?

Response: We thank the reviewer for this point. We have add the number of incident cases for each of the individual site-specific cancers to the table legends.

6. It would be useful if the authors could add some discussion on the grouping of obesity-related cancers. How robust and certain are these relationships and could other cancers be considered. In fact, it may be worth to conduct an analysis on all cancers to see whether there is indeed no association.

Response: For the present study we used cancers which were defined as obesity related by the World Cancer Research Fund (WCRF) (1). The WCRF has based this definition on information from the Continuous Update Project. This is an ongoing programme to analyse global research on how diet, nutrition, physical activity and weight affect cancer risk and survival. Among experts worldwide it is a trusted, authoritative scientific resource, which underpins current guidelines and policy for cancer

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prevention. For each obesity related cancer the WCRF has performed a systematic literature review and the results are available online (2). We have investigated all cancers which were defined as obesity-related by the WCRF. We have qualified the relationships as robust and certain since the relationships are based on systematic reviews. We have focused on these robust relationships only to avoid incidental findings. Furthermore, as different risk factors can have opposite relations to different forms of cancer, it is very hard to interpret an 'all-cancer' outcome. Therefore we did not perform an analysis on all cancers.

The grouping of the obesity-related cancers has some limitations. It is preferable to investigate each cancer type separately. However this was not possible for each cancer type due to a limited number of events. Since for all of the included cancers types in the present study robust associations were found with BMI in previous studies, it was in our opinion acceptable to perform these grouped analyses. We have changed the discussion concerning the grouping of obesity-related cancers into the following:
"Thirdly, the grouping of obesity-related cancers could be discussed. All different cancers were taken together as the number of total events would be too small when investigating each of the obesity-related cancers separately. Nevertheless, separate analyses would have been better."

1. http://www.wcrf.org/int/cancer-facts-figures/link-between-lifestyle-cancer-risk/weight-cancer
2. http://www.wcrf.org/int/research-we-fund/continuous-update-project-cup

7. The duration of follow-up is mentioned for non-sex-specific cancers, but not for the whole study. Can these be added to the abstract and results? Related to that, was there any loss to follow-up?

The number of included patients differs between the three analyses as different exclusion criteria were used. For the analyses of the total group of obesity-related cancers, patients diagnosed with a non sex-specific or sex-specific obesity-related cancer before entering the ZODIAC study were excluded (n = 2061 (2.9%)). For the non sex-specific analysis, only patients with a non sex-specific cancer before entering the ZODIAC study were excluded (n = 817 (1.1%)). For the sex-specific cancer analysis, only patients with a sex-specific cancer before entering the ZODIAC study were excluded (n = 1278 (1.8%)). Therefore it is not possible to present one follow-up for the whole study.

The duration of follow-up is described in the results section for the analyses of the total group of obesity-related cancers and for the analyses of the non sex-specific and sex-specific obesity-related cancers.

Total group of obesity-related cancers:
"The median follow-up period for these patients was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women."

Non sex-specific obesity related cancers:
"The median follow-up period was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women."

Sex-specific obesity-related cancers:
"The median follow-up period for these patients was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women."

There are small differences in the follow-up period between the different analyses, however rounded to 1 decimal place they are the same. We have added the following sentence to the abstract:
"The median follow-up period in all analyses was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women."

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We have used a dynamic cohort for the present study. Patients were only included if they have participated for at least one year in the ZODIAC project between 1998 and 2012. The follow-up time of each patient was defined by the time the patient was included in the ZODIAC project. For many patients the last check-up was before 2012 due to the fact they had died or had moved to another region in the Netherlands. These patients were not defined as lost to follow-up as the end of follow up for patients who were not diagnosed with cancer was also based on the last check up by their general practitioner.

8. It would be helpful to add the total number of incident cases within BMI categories to table 5.

Response: We have added the total number of incident cases within the BMI categories to table 5.

9. It is not very clear how the multiple imputation was conducted. Which variables were included in the imputation model and what package or procedure was used?

Response: We have changed the information concerning the multiple imputation into the following: "Multiple imputation analysis was performed for missing data on the independent variables, assuming that data was missing at random (MAR) or completely at random (MCAR). All variables of model 2 were included in the imputation model and the fully conditional specification model in SPSS was used to predict the missing data. Ten imputated datasets were created and the pooled results are presented."

10. Table 1: How was smoking defined? Did this include previous smokers?

Response: Information on smoking was collected during the check-up of the patient by the general practitioner or practice nurse as part of ZODIAC project whereby smoking was documented as yes or no. No data concerning previous smoking was documented in the ZODIAC project.

We added the following to the method section of the manuscript:
"Information on smoking was collected during the check-up of the patient by the general practitioner or practice nurse as part of the ZODIAC project whereby smoking was documented as yes or no. No data concerning previous smoking was available."

11. Table 1: A considerable proportion of patients was not on diabetes medication. This should be clarified. Does this mean that they were all on dietary interventions?

Response: These patients were on lifestyle interventions or on diabetes medication for which we did not have adjusted in the present study such as DDP-4 inhibitors or GLP-1 antagonists. 30.4% of the patients in the present study did not use metformine, SU-derivates or insulin. The exact number of patients on dietary interventions or other diabetes medication is unknown as we do not have these data. From other studies form the ZODIAC project we know that approximately 18% of the patients in the ZODIAC project do not use diabetes medication.

We have added the following sentence to the results section of the manuscript:
"30.4% of the patients did not use metformin, SU-derivates or insulin. These patients were on lifestyle interventions or other diabetes medication."

12. Tables: The units of measurement should be added for each covariable.

Response: We have added the unit of measurement of each covariable to the tables.

13. Which adjustments were made in Table 5?

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Response: The results in table 5 were adjusted for age, diabetes duration, HbA1c, serum creatinine, smoking status and the use of metformin, SU-derivatives and/or insulin. We have added this information to the table legend of table 5.

Reviewer: 2
Reviewer Name: Dr. Isaac Aladeniyi
Institution and Country: University of Ibadan, Ibadan, Oyo state, Nigeria.
Please state any competing interests: None declared

Great work but some unclear issues were observed, more in the methods.

1. With regards to the study design, there appear to be no reference group in this study for ease comparison of the risk. We may ask, could this risks as enumerated in this study be same among type 1 D.M patients or perhaps with the general population?

Response: First of all, we want to thank the reviewer for his valuable comments.
According to the World Cancer Research Fund, being overweight or obese is related to an increased incidence of oesophageal, stomach (cardia), colorectal, liver, gallbladder, pancreatic and kidney cancer in both sexes in the general population. Furthermore, being overweight or obese is related to an increased incidence of ovarian, endometrial and postmenopausal breast cancer in women and to advanced prostate cancer in men in the general population. Whether there is an association between body mass index (BMI) and excess risk of developing obesity-related cancers in patients with type 2 diabetes is unclear. Type 2 diabetes itself is also related to a higher cancer risk. Whether this increased risk is directly related to type 2 diabetes, caused by longer periods of hyperglycaemia and/or elevated insulin levels, or indirectly, due to common risk factors like obesity, is not clear. We hypothesised that BMI and T2D are synergetic in their relation to obesity-related cancers, based on the idea that BMI and T2D are both risk factors for obesity-related cancers through the same (obesity-related) pathway. Therefore we think that the risk as enumerated in this study is not the same as in the general or in type 1 diabetic populations.

2. The method of patient selections were also not clearly enumerated. It may be interesting to know, if other risk factors that are possible confounders for some of the cancers of interest in the patients selected were considered and how they were addressed, particularly in the analysis.
All of the confounders for which we have adjusted are presented in tables 2,3 and 4. All confounders were derived from the ZODIAC project. This project started in 1998 and was part of a study at that time that primarily investigated the effects of shared care in patients with type 2 diabetes treated in primary care in the Zwolle region of the Netherlands. Only diabetes related variables are collected in the ZODIAC project. Except for the included variables and the use of alcohol, no other cancer-related confounders were considered as no data was available for these confounders. We did not use alcohol consumption as a confounder since alcohol consumption was poorly registered.

Response: We have added a flowchart to the method section to clarify the method of patient selection (fig 1).

3. The method of diagnosis of the patients in the study should be mentioned, particularly, for the cancer cases, were they all autopsies or clinical conclusions by physicians?

Response: We agree with the reviewer that we should add this information to the method section. Therefore we have added to following sentences to the manuscript:

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“The diagnosis of type 2 diabetes was based on the guidelines of the Dutch College of General Practitioners (twice a fasting plasma glucose level ≥ 7 mmol/l or once a non-fasting plasma glucose level ≥ 11.1 mmol/l accompanied by symptoms of hyperglycemia).”

And

“All included cancer cases were histologically confirmed by a pathologist.”

4. Data collected for this study may need to be mentioned because the paper only mentioned data collected by ZODIAC and NKR.

Response: In the section ‘data collection’ we described the data of the ZODIAC and the NKR which we have used for the present study. We agree with the reviewer that this could be described in more detail. Therefore we have changed this section into the following:
“For the current study a database was constructed which consisted of both the variables of the ZODIAC project and the variables of the NKR. The demographic and clinical data which were used in the present study were collected as part of ZODIAC project and included: sex, age, diabetes duration, HbA1c, serum creatinine, BMI, smoking status and the use of metformin, sulfonylurea derivatives and insulin. Information on smoking was collected during the check-up of the patient by the general practitioner or practice nurse as part of ZODIAC project whereby smoking was documented as yes or no. No data concerning previous smoking was documented. Baseline was defined as the first year that a patient was included in the ZODIAC project. Cancer characteristics provided and collected by the NKR were: cancer origin, incidence date, TNM stage, morphology and type of therapy.”

5. In categorising BMI in line 6 under statistical analysis, the demarcation between the groups overlapped, this may create a problem of misclassification of patients and thus affect analysis.

Response: Thank you for noticing. This is a typing error. In the analyses this overlapping has not occurred. We have changed this sentence into the following:
“For the analyses of BMI as a categorical variable, four BMI categories were used (≥ 18.5 - < 25.0 kg/m2, ≥ 25.0 - < 30.0 kg/m2, ≥ 30.0 - < 35.0 kg/m2, ≥ 35.0 kg/m2).”

6. I suppose that your conclusion is rather too emphatic and ambitious, given the fact of your claim as the first to conduct this study on the a large scale and your study design. I suggest you tone down a little. Further studies with advanced method may support your findings in future.

Response: After discussion and careful reconsideration we agree with the reviewer that our conclusion is somewhat emphatic and ambitious. Therefore were have changed the conclusion into the following:
“In men with type 2 diabetes mellitus BMI is associated with the total group of obesity-related cancers and with non sex-specific obesity-related cancers. However, BMI is not related to advanced prostate cancer. The present study provides an extra argument for questioning advanced prostate cancer being obesity-related, at least in men with type 2 diabetes.
In women, BMI is associated with the total group of obesity-related cancers and with ovarian, endometrial and postmenopausal breast cancer. BMI is not related to non sex-specific obesity-related cancers in women with type 2 diabetes.”

We have changed the conclusion of the abstract into the following:
“BMI is associated with obesity-related cancers in men with type 2 diabetes, except with advanced prostate cancer. The results of this study provide reason to reconsider the classification of advanced prostate cancer as an obesity-related cancer, at least in type 2 diabetes. In women, BMI is associated with the total group of obesity-related cancers and with sex-specific obesity-related cancers.”

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7. I suggest the author should review the methods, it's a good study worthy of publication.

We have rewritten the method section. Hopefully it is now in line with the expectations of the reviewer. Please let us know if you have other recommendations.

Reviewer: 3
Reviewer Name: Gisele M Carriere, Senior Social Science Researcher
Institution and Country: Statistics Canada, Health Analysis Division, Canada
Please state any competing interests or state: None declared

Thank you for the opportunity to review your research. These results are an important contribution to this area of epidemiology since your results demonstrate the complexity of interaction of patient sex and type of cancer in the relation of BMI to obesity-related cancer incidence. I have the following comments:

1. Others previously and yourselves have also indicated that BMI and type 2 diabetes may confound associations to cancer incidence. Although you state that more specific obesity-related cancer sites (within all obesity-related cancers) were too small to analyse, your discussion on page 13 regarding sex differences in the association of BMUI and non sex-specific obesity-related cancers had me wondering about results for gastrointestinal cancers (or at least gastric-cardia). If that number were reportable, and sex differences remained, it would further support sex-differences for adiposity as plausible
explanation.

Response: The numbers of cancer of the gastric-cardia (5 women and no men) are far too low for an informative analysis of these data. We did performed an analysis for the relationship between BMI and colorectal cancer in and men and in women (311 events in women, 368 events men). In both men and women no association between BMI and colorectal cancer was found. Please let us know if you think that it is informative to add these results to our manuscript.

2. How many cases from the ZODIAC-project did NOT link to the cancer registry? It would be good to report the number of linked cases as a percentage of the cases included for study after linkage.

Response: We do not know the exact number of patients which could not be linked to the Netherlands Cancer Registry (NKR). The cancer registry only consist of patients who are diagnosed with cancer. Therefore only patients with type 2 diabetes and cancer could be linked to the cancer registry. Patients with type 2 diabetes who could not be linked to the cancer registry do not have cancer or could not be linked due to a registration error.
The linking was performed by a trusted third party using postal code, full name, date of birth and sex. The NKR expects that the number of false-positive and the number false-negative for the ZODIAC-NKR linkage is both under 1%.

We have added the following information to the method section:
“The linking was performed by a trusted third party using postal code, full name, date of birth and sex. The NKR expects that the number of false-positive and the number false-negative for the ZODIAC-NKR linkage is both under 1%.”

3. Small edit required on page 9, second paragraph, second line:" .... with a non-obesity-related cancer before during follow-up." Was it "before" or 'during" ?

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We thank the reviewer for noticing. We have changed this sentence into the following:
“Patients were not censored if they were diagnosed with a non-obesity-related cancer during follow-up.”

VERSION 2 – REVIEW

REVIEWER	Sanne Peters The George Institute for Global Health, University of Oxford
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	The authors have satisfactory addressed the previous comments. I have no further comments.

REVIEWER	Dr. Isac Aladeniyi University of Ibadan, Ibadan, Oyo state, Nigeria
REVIEW RETURNED	15-Nov-2017

GENERAL COMMENTS	The author may wish to clarify the actual sample size used for the study as three different information were given in this regard (line 21 of abstract, 52,044 type 2 D.M patient was quoted; line 12 of summary/ strength of study, 71,634 type 2 D.M was quoted as samples a line 15 &16 of material/ method, 71,634 was quoted as the total recorded cancer cases in NKR. Line 52, the author recorded 1989 instead of 1998 as previously stated. This study did not at anytime provide background information about the incidence of the cancers under study in the general population. i perceive that the background incidence in population will make bold the risk of these diseases in the study population.

REVIEWER	Gisele M Carriere, Senior Social Science Researcher Statistics Canada, Canada
REVIEW RETURNED	09-Nov-2017

GENERAL COMMENTS	Important contribution to the literature, thank you for the opportunity to review this.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sanne Peters
Institution and Country: The George Institute for Global Health, University of Oxford Please state any competing interests: None declared

Comment: The authors have satisfactory addressed the previous comments. I have no further comments.

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Response: We would like to thank the reviewer for her time spent on reviewing our manuscript and for her
recommendation to publish our manuscript.

Reviewer: 2
Reviewer Name: Dr. Isac Aladeniyi
Institution and Country: University of Ibadan, Ibadan, Oyo state, Nigeria Please state any competing interests: None

1. The author may wish to clarify the actual sample size used for the study as three different information were given in this regard (line 21 of abstract, 52,044 type 2 D.M patient was quoted; line 12 of summary/ strength of study, 71,634 type 2 D.M was quoted as samples a line 15 &16 of material/ method, 71,634 was quoted as the total recorded cancer cases in NKR.

Response: First of all, we would like to thank the reviewer for his time spent on reviewing our manuscript and for his recommendation to publish our manuscript.

We could imagine that it is confusing that it seems like that we have used different sample sizes. A dataset of 71.634 patients with type 2 diabetes was linked to the Netherlands Cancer Registry. However not all of these patients were included in the present study. After exclusion of some patients, 52.044 patients were included in the present study. So this explains the difference between the sample size as quoted in the abstract and in the bullet points.

We have changed one of the bullet point into the following:
“A dataset of 71.634 patients with type 2 diabetes was linked to the Netherlands Cancer Registry to obtain data on cancer incidents and finally 52.044 patients were included in the present study.”

In the material and method section the same 71.634 patients were quoted. Not all of these patients were diagnosed with cancer. We have changed this sentence into the following:
“The combined ZODIAC-NKR database contains 71.634 patients, of which 10717 (15%) were diagnosed with cancer.”

2. Line 52, the author recorded 1989 instead of 1998 as previously stated.

This is not a typing error. The ZODIAC project started in 1998. The Netherlands Cancer Registry (NCR) started in 1989. For the current manuscript we also used the data from the NCR in the period before 1998 (from 1989 to 1998). We have used this information to exclude patients who were diagnosed with a non sex-specific or sex-specific obesity-related cancer before entering the ZODIAC study.

Response: We have changed this section into the following:
“For the current study, available information on clinical variables from patients participating for at least one year in the ZODIAC project between 1998 and 2012 was linked to available information of the Netherlands Cancer Registry (NKR) to obtain data on cancer incidents in the years between 1989 and 2012. Information from the NKR in the period before 1998 was used to exclude patients who were diagnosed with an obesity-related cancer before entering the ZODIAC study.”

3. This study did not at anytime provide background information about the incidence of the cancers under study in the general population. I perceive that the background incidence in population will make bold the risk of these diseases in the study population.

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Response: We did indeed not present background information about the incidence of the cancers under study in the general population. It was not our aim to investigate the incidence of obesity-related cancers in a population with T2D and to compare this incidence with the incidence in the general population. Our aim was to investigate whether there is still an association between BMI and obesity-related cancers in patients with T2D. For this research question, presenting the incidence rates in the general population is in our opinion less relevant. We agree with the reviewer that it could bold the risk of these diseases in the study population. However, the fact that BMI is associated with even eleven different cancer types in the general population is in our opinion already showing enough relevance. Adding the incidence for each of the eleven obesity related cancers separately to the introduction would in our opinion result in an introduction which is unnecessarily longer and less to the point. Therefore we have chosen not to present these incidence rates.

Reviewer: 3
Reviewer Name: Gisele M Carriere, Senior Social Science Researcher Institution and Country: Statistics Canada, Canada Please state any competing interests: None declared

Comment: The authors below Important contribution to the literature, thank you for the opportunity to review this.

Response: We would like to thank the reviewer for her time spent on reviewing our manuscript and for her
recommendation to publish our manuscript.

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