

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Sex differences in survival of patients with type 2 diabetes in primary care (ZODIAC-50).
AUTHORS	Hendriks, Steven; van hateren, Kornelis; Groenier, Klaas; Landman, Gijs; Maas, Angela; Bilo, Henk; Kleefstra, Nanne

VERSION 1 - REVIEW

REVIEWER	Tomás Vega Alonso Public Health Directorate. Junta de Castilla y León. Valladolid Spain
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	<p>The authors present a survival analysis in a cohort of diabetes mellitus type 2 patients in primary care in comparison with the general population to explore differences between sex. In my opinion the research question is correct and the methods and results well described. However, some minor questions should be clarified by the authors</p> <p>In methods: It is not clear for me how the authors use the lineal interpolation to estimate the median survival in the study population. The same for the extrapolation and interpolation in the general population. Although you have stated the Ethical Committee approval in the reference 11, in my opinion it could be also mentioned in this section, as well as if you have asked for patients' informed consent.</p> <p>In discussion: The authors could address the following questions: Can the differences between men and women in the median survival be explained by the mean age differences or by the diabetes duration? Discuss that if necessary. In discussion you say that 'under-treatment of women could explain the lower survival rate', but in your cohort, women are more frequent treated with insulin than men (more diet). Can that be due to the different severity or duration of the diabetes? Can you discuss the differences between the population in which the diabetes patients were recruited (Zwolle region) and the general population of the Netherland used for mortality comparisons?</p>
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REVIEWER	Antonino Catalano University of Messina, Messina, Italy
REVIEW RETURNED	02-Apr-2017

GENERAL COMMENTS	In a large prospective cohort observational study, the authors investigated sex differences in survival of patients with type 2 diabetes. A decrease in median survival in T2DM with in comparison with general population was confirmed, and only for T2DM patients without a history of CVD, a significantly lower relative survival in women compared to men with T2DM was found. Their findings are not really new, but they offer a picture of primary care treated diabetic patients in the Netherlands.
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REVIEWER	Araz Rawshani University of Gothenburg Sweden
REVIEW RETURNED	17-Jun-2017

GENERAL COMMENTS	<p>Frankly, this is a very good paper, written very clearly and I have no serious objections, but a few minor coments.</p> <p>I think that you have done a great job to review the literature. Indeed there are much less data focusing on primary care patients and their relative survival, which is why this paper is of great relevance.</p> <p>The methods are clearly written and appears to be sound. The use of relative survival is also appropriate. The subgroups were wisely constructed such that they actually answer clinical questions (despite the lack of covariate adjustment).</p> <p>I have a few minor comments.</p> <p>There may be, at least compared with the other published studies (which typically includes patients in secondary care), some survival bias here. It's not serious but it must be mentioned in the paper. The study is limited to primary care patients, which means that the most problematic patients have been excluded. Secondly, at the enrollment (according to the Methods section) the general practitioners were allowed to exclude patients with T2DM if they were believed to have a low expected survival. So frail patients were excluded as well. This leaves quiet a strong population with T2DM. This should be mentioned in the limitations.</p> <p>You should then stress the fact that even when only viewing primary care and removing patients with frailty, patients with t2dm survive 2–2 years less and it appears to be confined to patients with CVD risk</p>
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	<p>factors.</p> <p>Secondly, you have not presented the number of deaths in the subgroups, which may affect the power of those analysis. This too should be mentioned and presented.</p> <p>Third, this is one of few studies showing that elderly with T2DM are actually at higher risk of death than the general population. Several recent studies have shown opposite results, i.e. the older patients with T2DM having better survival than younger t2dm patients. This should be discussed briefly.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Tomás Vega Alonso

Institution and Country: Public Health Directorate. Junta de Castilla y León, Valladolid, Spain

Competing Interests: None declared

The authors present a survival analysis in a cohort of diabetes mellitus type 2 patients in primary care in comparison with the general population to explore differences between sex. In my opinion the research question is correct and the methods and results well described. However, some minor questions should be clarified by the authors

In methods:

1. It is not clear for me how the authors use the lineal interpolation to estimate the median survival in the study population. The same for the extrapolation and interpolation in the general population.

First of all, we want to thank the reviewer for his valuable comments.

We used the following formula to estimate the median survival:

$$X2 \text{ (median survival)} = ((Y2 - Y1) (X3 - X1) / (Y3 - Y1)) + x1$$

Whereby (using men as an example):

X1 = the follow-up year in which more than 50% was still alive at the end (for men in our cohort, the 13th follow-up year

X3 = the follow-up year in which less than 50% was still alive at the end (for men in our cohort, the 14th follow-up year

Y1 = the cumulative survival at the end of X1 (for men cumulative survival 13th follow-p year = 0.5294 (rounded of 0.53)

Y2 = the median (= cumulative survival of 0.5)

Y3 = the cumulative survival at the end of X3 (for men cumulative survival 14th follow-p year = 0.4945)

$$\text{Median survival of men with T2D} = ((0.5 - 0.5294) (14 - 13) / (0.4945 - 0.5294)) + 13 = 13.8424$$

(rounded of 13.8).

For the general population, linear extrapolation with the average difference between the cumulative survivals of the general population was conducted first, before using linear interpolation to estimate the median survival. We had to do that because after 14 years of follow-up, still more than 50% of the general population was alive (for men after 14 years the cumulative expected survival was 0.56). For identifying X1, X3, Y1 and Y3 of the general population we used the following steps:

1. We calculated the average difference between the cumulative survivals of the 14 follow-up years (for men in our study population 0.031054).
2. We extrapolated the cumulative survival by extracting this average difference from the cumulative survival of the previous year (see table 1 in additional file 1) (unfortunately it was not possible to add a table to the reply to the reviewers text box).
3. Finally we measured the median follow-up by using the estimated cumulative survival of the 16th and 17th follow-up year.

We can imagine that readers of our manuscript also want to know how we used the linear interpolation. Therefore we have added this explanation as a supplemental file to the manuscript and referred to this additional file in the main text:

“An estimation of the median survival of the study population was calculated using linear interpolation. For the general population, linear extrapolation with the average difference between the cumulative survivals of the general population was conducted first, before using linear interpolation to estimate the median survival (see additional file 1).”

2. Although you have stated the Ethical Committee approval in the reference 11, in my opinion it could be also mentioned in this section, as well as if you have asked for patients' informed consent.

The ethical approval is presented on page 15 of the manuscript.

“This study was approved by the local ethical committee of Isala, Zwolle, the Netherlands. All patients gave written informed consent.”

We added this sentence to the method section as well, as suggested by the reviewer.

In discussion:

The authors could address the following questions:

3. Can the differences between men and women in the median survival be explained by the mean age differences or by the diabetes duration? Discuss that if necessary.

The relative survival decreases with increasing age (see age subgroups table 3).

The relative survival also decreases with increasing diabetes duration (data not shown). The differences between men and women in the median survival could therefore possibly be explained by both the higher age and longer diabetes duration in women with T2D.

Nevertheless, even now that women have a higher age and longer diabetes duration, there is still no significant difference in relative survival between men and women. In other words, when women would have the same age and diabetes duration, the difference in relative survival would possibly be smaller. This strengthens our conclusion that in the total population there is no significant difference in relative/median survival.

We added the following to the discussion section of the manuscript:

“The differences in relative survival between men and women in the total study population could possibly be explained by both the higher age and longer diabetes duration in women with T2D.

Although women have a lower relative survival, it is not significantly lower compared to men. When women would have the same age and the same diabetes duration as men, the difference in relative survival would likely be smaller. This strengthens our conclusion that in the total population there is no significant difference in relative survival between sexes.”

4. In discussion you say that ‘under-treatment of women could explain the lower survival rate’, but in your cohort, women are more frequent treated with insulin than men (more diet). Can that be due to the different severity or duration of the diabetes?

The higher use of insulin could be the result of the longer duration of diabetes in women. Nevertheless, with under-treatment of women we meant differences in the use of lipid lowering drugs and aspirin (reference 19). Differences in the use of lipid lowering drugs and aspirin are suggested as explaining factors for sex differences in survival. These drugs were less used in women in our cohort. However this is probably not due to under treatment as women in our cohort have a lower Cholesterol HDL ratio and had fewer cardiovascular incidents compared to men.

5. Can you discuss the differences between the population in which the diabetes patients were recruited (Zwolle region) and the general population of the Netherland used for mortality comparisons?

It is difficult to discuss the differences between our cohort and the general population since we did not use a specific cohort from the general population. The survival of the patients with T2D was compared with the expected survival of men and women with the same age from the general population in the Netherlands. These survival rates were derived from mortality rates of subjects from the entire nation. Besides age and sex, there was no clinical data available of this population. Therefore it is hard to discuss differences between both. Although no specific indications exist which suggests that people in the Zwolle region are healthier or unhealthier compared to the whole population in the Netherlands, we do not know that for sure. It would have been better if we had used a control population from the Zwolle region, but unfortunately we did not have the availability of such a control population.

We changed the limitation section of the discussion into the following:

“Second, although no specific indications exist which suggests that people in the Zwolle region are healthier or unhealthier compared to the whole population in the Netherlands, we do not now that for sure. It would have been better if we had used a control population from the Zwolle region, but unfortunately such a control population was not available.”

Reviewer: 2

Reviewer Name: Antonino Catalano

Institution and Country: University of Messina, Messina, Italy

Competing Interests: None declared

In a large prospective cohort observational study, the authors investigated sex differences in survival of patients with type 2 diabetes. A decrease in median survival in T2DM with in comparison with general population was confirmed, and only for T2DM patients without a history of CVD, a significantly lower relative survival in women compared to men with T2DM was found. Their findings are not really new, but they offer a picture of primary care treated diabetic patients in the Netherlands.

We would like to thank the reviewer for reviewing our manuscript and for his recommendation to publish our manuscript.

Reviewer: 3

Reviewer Name: Araz Rawshani

Institution and Country: University of Gothenburg, Sweden

Competing Interests: None declared.

Thank you for this clearly written and interesting paper. Frankly, this is a very good paper, written very clearly and I have no serious objections, but a few minor comments.

I think that you have done a great job to review the literature. Indeed there are much less data focusing on primary care patients and their relative survival, which is why this paper is of great relevance. The methods are clearly written and appears to be sound. The use of relative survival is also appropriate. The subgroups were wisely constructed such that they actually answer clinical questions (despite the lack of covariate adjustment).

I have a few minor comments.

1. There may be, at least compared with the other published studies (which typically includes patients in secondary care), some survival bias here. It's not serious but it must be mentioned in the paper. The study is limited to primary care patients, which means that the most problematic patients have been excluded. Secondly, at the enrollment (according to the Methods section) the general practitioners were allowed to exclude patients with T2DM if they were believed to have a low expected survival. So frail patients were excluded as well. This leaves quite a strong population with T2DM. This should be mentioned in the limitations.

You should then stress the fact that even when only viewing primary care and removing patients with frailty, patients with t2dm survive 2–2 years less and it appears to be confined to patients with CVD risk factors.

We agree with the reviewer that selection of patients from primary care causes bias. We have already mentioned this fact in the limitation section but we have not used the term bias explicitly. Therefore we changed a part of the limitation section into the following:

“Fifth, selection bias has occurred in this study. The study population consisted only of patients with T2D who are treated in primary care. Patients in secondary care often have worse manifestations of T2D and more often macrovascular disease and will probably have a lower survival. Furthermore, patients with a very short life expectancy or insufficient cognitive capabilities were also excluded from participation.”

We also agree with the reviewer that we should stress the fact that the survival of this primary care group is only 2 to 3 years lower. Therefore we changed the last part of the limitation section into the following:

“Although these limitations imply that the generalizability of our results is limited to primary care, it is still representative for a large part of the T2D population due to the fact that the majority (>85%) of the patients with T2D is treated in primary care in the Netherlands (26). In this group of patients with T2D, the survival is only 2.2 years lower in men and 3.5 years lower in women compared to men and women in the general population. In patients with T2D with no microvascular complication and in patients with a low risk profile, even no difference in relative survival compared to the general population was found.”

2. Secondly, you have not presented the number of deaths in the subgroups, which may affect the power of those analysis. This too should be mentioned and presented.

We agree with the reviewer that we should present the number of deaths in the subgroups. We have added the number of deaths and the number of lost to follow-up to table 3. Furthermore we have added the following sentence to the limitation section of the manuscript:

“Fourth, the number of patients in subgroups was sometimes relatively low which has decreased the precision of the estimates.”

3. Third, this is one of few studies showing that elderly with T2DM are actually at higher risk of death than the general population. Several recent studies have shown opposite results, i.e. the older patients with T2DM having better survival than younger t2dm patients. This should be discussed briefly.

The reviewer points out that survival in elderly patients with T2DM in primary care in the Netherlands is different compared to other countries. Providing a simple explanation for this observation probably is impossible, but we have some suggestions:

It could be caused by differences in duration of diabetes between our study and those studies. The older population in our study has a longer duration of diabetes than the younger population, which in turn could translate into a more pronounced effect of duration of diabetes itself on mortality risk.

The patients with type 2 diabetes were solely derived from primary care. It could be that younger people with complications or a complicated (co-morbid) disease are referred to secondary care relatively earlier and more than older patients in similar conditions. With this in mind, it is hard to draw a sufficiently reliable conclusion for the total population on mortality rates of younger vs older people with T2DM. Currently, we are in the process of starting the same process of data collecting in secondary care, with the participation of 42 hospitals in the Netherlands. Regretfully, it will take years before being able to address the rightful question of the reviewer on this subject.

VERSION 2 – REVIEW

REVIEWER	Tomás Vega Public Health Directorate. Junta de Castilla y León, Valladolid, Spain
REVIEW RETURNED	18-Jul-2017

GENERAL COMMENTS	The authors have addressed most of the suggestions and comments made by the reviewers and made the appropriate changes. In my opinion the paper can be published
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