Author’s response to reviews

Title: The impact of cancer on diabetes outcomes.

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Author’s response to reviews:

Dear Editor

Thank you very much for having read our article so carefully. We have now worked thoroughly through the manuscript and revised it according to the comments.

We have attached a “clean version” of the manuscript: “Main Document_R3.1_clean”. The point-by-point answers are inserted in a copy of the comments below.

We look forward to hearing from you again.

On behalf of all authors.

Yours sincerely

Anne Arreskov

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Dear Mrs Arreskov
Your manuscript "The impact of cancer on diabetes outcomes." (BEND-D-18-00226R3) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Endocrine Disorders, once you have carried out some essential revisions.

1. We note that you have indicated that verbal consent had been obtained from all participants. We ask that you please provide details in your Ethics statement explicitly describing whether the need for written informed consent had been wavered by the relevant ethics institution/committee which approved of your study.

Answer: thank you for your comment. We have provided further details about Ethics at P. 13 LI 321-328:

"The DCGP study was an open, cluster-randomized, controlled trial of the effect of intensified diabetes management. Taking written information about the study as a starting point, all patients gave verbal informed consent to participate, following a dialogue with their GP, where the patients could ask questions. When the study started in 1988 it was generally accepted to seek oral informed consent only, and this procedure was approved by The Copenhagen and Frederiksberg Research Ethics Committee (ClinicalTrials.gov NCT01074762). The study was performed in accordance with the Helsinki Declaration. The study adheres to CONSORT guidelines"

2. While assessing your manuscript in-house, we found that there remain several instances where the text displayed similarities to text found in other previously published sources. While we understand that you may wish to express some of the same ideas contained in these publications, please be aware that we cannot condone the use of text from previously published work. We would therefore be grateful if you could reformulate the sections listed below to resolve the overlap between your manuscript and other sources. Please ensure that, where relevant, these sources are also referenced as appropriate.

The overlap primarily occurs between your submission and the following previously published sources:

The impact of gender on the long-term morbidity and mortality of patients with type 2 diabetes receiving structured personal care: a 13 year follow-up study

https://link.springer.com/article/10.1007%2Fs00125-015-3804-4

The development of multimorbidity during 16 years after diagnosis of type 2 diabetes

https://journals.sagepub.com/doi/10.1177/2235042X18801658
The excess mortality of patients with diabetes and concurrent psychiatric illness is markedly reduced by structured personal diabetes care: A 19-year follow up of the randomized controlled study Diabetes Care in General Practice (DCGP)

This overlap mainly exists in the Methods section.

Please note that an abundance of overlapping text may preclude a given manuscript from publication. Therefore, we ask that you please rephrase these sections to minimise overlap and prevent future delays in the editorial process for your manuscript.

ANSWER:

Thank you for your comments and accuracy. The Methods section has been revised, and the tree articles have been referred to P. 4 line 94-189:

"Methods

The DCGP study was a cluster-randomized, open, controlled trial of the effect of intensified diabetes management (ClinicalTrials.gov NCT01074762), and the study adheres to CONSORT guidelines. A total number of 474 GPs volunteered to participate. Practices were randomly allocated to provide either routine care or structured personal care to their patients, who were newly diagnosed with type 2 diabetes. A description of the study design has also been reported earlier [16-18].

Patients

The GPs included all of their patients who were 40 years or older and diagnosed with diabetes during the inclusion period. At a major laboratory, the diabetes diagnosis was confirmed by a single fasting whole blood/plasma glucose concentration (≥7.0/8.0 mmol/l). The protocol-based exclusion criteria were: unwillingness to participate, severe psychiatric disease or life-threatening somatic disease (Fig. 1). As previously reported, the randomization was balanced [16, 17]. In total 1,369 (99.1%) of 1,381 patients in the final study population were of Western European descent. Approximately 97.5% of the patients were classified as type 2 diabetes patients, which was based on the onset of insulin treatment. The Frederiksberg and Copenhagen Research Ethics Committee approved the study.

Intervention

The follow-up of patients in the intervention group consisted of examinations every three months and annual screening for diabetes complications. These examinations were facilitated by a questionnaire forwarded to the GP one month before the next expected consultation. The GP together with the patient was asked to define optimal goals for controlling important risk factors
within three categories: ‘good,’ ‘acceptable,’ and ‘poor’ control. The emphasis was on glycemic control. At each quarterly consultation, GPs should compare the patient’s achievements with the goal and consider changing either goal or treatment accordingly. In overweight patients, the GP was prompted to agree with the patient on a small, realistic weight reduction, and this agreement should be recorded and followed up. However, participants were not required to target a particular body weight [16].

Through folders and leaflets for both physicians and patients, annual descriptive feedback reports on individual patients as well as six annual half-day seminars, GPs were introduced to possible solutions to therapeutic problems in the intervention group.

Generally, the importance of diet was stressed, and if possible, the GPs were recommended to postpone the start of glucose-lowering drugs until at least three months after diabetes diagnosis, to observe the effect of any weight loss. Further, the GPs were also prompted to recommend increased physical exercise and simple dietary rules [16, 17]. In cases of persistent hyperglycemia, metformin was recommended for patients who were overweight by clinical judgment. Glipizide or glibenclamide was suggested for patients of normal weight, and tolbutamide was recommended in patients older than 70 years. If the goal for blood glucose was not achieved and before starting insulin, a combination of metformin and a sulfonylurea was suggested as the last step. The preferred treatments for patients with hypertension were ACE-inhibitors or β-blockers; however, for patients with heart failure furosemide was preferred, and for patients older than 70 years thiazides were recommended. In cases of diet-resistant dyslipidemia, lipid-lowering drugs were recommended. To individualize the treatment, the GPs were allowed to deviate from the recommendations.

During the intervention phase, the GPs in the routine care group were free to choose any treatment and also to revise it. [16]. The intervention was terminated on 26 September 1995, and the six-year examination was initiated. The study coordinators did not contact routine care practices during the intervention period after recruitment was completed and no attempt was made to maintain patients in randomized groups or to influence their therapy in the post-intervention period.

Clinical and Registry-Based follow-up

After median (IQR) 5.57 (4.96-6.16) years in the structured personal care group and after 5.85 (5.30-6.45) years in the routine care group, a clinical follow-up examination was completed for 970 (93.4%) of 1039 surviving patients (Appendix 1). A description of all variables and definitions has previously been published [16-19].

Using the unique identification number assigned to all Danish residents in the Danish Civil Registration System, emigration and vital status of all patients were ascertained. This enabled unambiguous linkage between the study population and the Danish national registries [20]. On 31 December 2008, all surviving patients were censored. The Danish Register of Causes of Death supplied information about possible and underlying contributory causes of death [21]. In four patients, the cause of death was not recorded. Information on cancer diagnoses was obtained
from The Danish Cancer Registry [22], however non-melanoma skin cancer and some ill-defined cancers were not included in our cancer diagnosis (Additional Table 1). The Danish National Patient Register gave information on contacts with hospitals in Denmark, e.g., surgical procedures performed and discharge diagnoses [23]. These registries provided information on the predefined outcomes: all-cause mortality, diabetes-related deaths, any diabetes-related endpoint, stroke, myocardial infarction, microvascular disease, and peripheral vascular disease [16] (Additional Table 2).

Statistical Analysis

The incidence rates of the outcomes defined above were compared between structured care and routine care with hazard ratios (HRs) from Cox regression models on time from diagnosis to the first occurrence of the outcome; death and end of follow-up were censoring events. In these models, the accrual of a cancer diagnosis was modeled as a time-varying covariate. These comparisons were performed for patients with and without a cancer diagnosis separately to be able to assess whether there is a differential effect. Concurrently, in an auxiliary Cox regression analysis, the incidence rates for cancer were compared between structured care and routine care; these incidences are visualized in Kaplan-Meier curves. If a patient had an occurrence of an outcome before the diabetes diagnosis, this patient was excluded from the analyses about that outcome. In all assessments, we used a robust sandwich estimator to determine 95% CIs and P values to adjust for the clustering of patients within practices [24]. We further adjusted the comparisons for the following variables, assessed at diagnosis: sex, age, body mass index, hypertension, diagnostic fasting plasma glucose, total cholesterol, living alone, basic school education, sedentary physical activity, and current smoking. Incidence rates were calculated as the number of patients experiencing the corresponding outcome divided by the total person-time at risk. Patients with missing values in one or more variables were omitted from analyses where these variables were included.

Comparisons between structured care and routine care were done according to the intention-to-treat principle. Analyses were done using SAS (version 9.4). The level of statistical significance was 5%.

3. Please include the date of trial registration with the Trial registration number in the abstract. If the date of registration is after the date that the first participant was recruited, please also state ‘retrospectively registered’.

Answer: the date is now included in the abstract p. 3 L 51-53.

"TRIAL REGISTRATION: The Copenhagen and Frederiksberg Research Ethics Committee approved the study (DCGP was retrospectively registered February 24, 2010, at ClinicalTrials.gov NCT01074762). " 
4. When submitting your revised manuscript please ensure you do so as a single clean copy without any tracked changes, colored or highlighted text, as these are no longer required at this stage of the editorial process.

Once you have made the necessary corrections, please submit a revised manuscript online at:

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A point-by-point response letter must accompany your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, line 12, page 5). If you disagree with any comments raised, please provide a detailed rebuttal to help explain and justify your decision.

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Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

A decision will be made once we have received your revised manuscript, which we expect by 27 Apr 2019.
We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Matthew P. Hickey

on behalf of Amber West
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