Author's response to reviews

Title: Diabetes is not a risk factor for the carpal tunnel syndrome

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Author's response to reviews: see over
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Version: 3 Date: may 2014
Dear editor,

First of all, we want to thank you for your interest in our manuscript and the opportunity to submit a revised version. We also thank the reviewers for their constructive comments and suggestions, which have resulted in an improvement of our manuscript. Please find below the point-by-point reply to your comments.

Reviewer 1

Title: Diabetes is not a risk factor for the carpal tunnel syndrome
Version: 2 Date: 10 April 2014
Reviewer: Russell Gelfman
Reviewer’s report:

This is a case-control study of all patients with CTS seen between January 2011 and July 2012 and unmatched controls seen with a diagnosis of HNP between the same dates.

Major Compulsory Revisions

For those not familiar with the Isala clinics, a brief description of the setting and patient population would be helpful. Who is referred to the clinic and why? Is everyone in the community with CTS and HNP referred here? We need to know this in order to assess the possibility of referral bias.

The Isala is a general, non-academic teaching hospital in the North East of the Netherlands with a catchment area of approximately 800,000 inhabitants. The Isala delivers all kinds of care to patients who are referred by the general practitioners in the Zwolle region of the Netherlands. Recently the name of the Isala clinics is changed in Isala, so we applied this change in this manuscript as well.

All patients with symptoms of CTS or HNP which could not be treated by the general practitioner with conservative treatment are referred here to the department of neurology or plastic surgery. Patients with symptoms of CTS may have had a brace or injections with corticosteroids before they were referred to the Isala.

The setting and study population (first sentences of the methods section of this manuscript) have been changed to be more explicit:

(page 4, line 78) “This study was conducted at the Isala, a general hospital with a catchment area of 800,000 inhabitants in the North East of the Netherlands. All patients with severe symptoms of CTS or with symptoms which could not be treated by a general practitioner with a conservative approach (i.e. watchful waiting, a brace or corticosteroid injections) and who were referred to the outpatient clinic of the Isala between January 2011 and July 2012 were identified.”

The CTS group appears to contain patients with both Type 1 and Type 2 DM. The control group only contains patients with Type 2 DM. Type 1 and Type 2 DM are thought to be two different diseases. Those with Type 1 DM should either be excluded or the control group needs to have additional patients with Type 1 DM and this needs to be analyzed as a separate potential risk factor. The present analysis would suggest that both Type 1 and Type 2 are not risk factors for CTS and this would be misleading.
The reviewer is right. There were only 10 patients with type 1 diabetes in de CTS and 0 patients with type 1 diabetes in the HNP group. We excluded all patients with type 1 diabetes as suggested by the reviewer. Furthermore, we excluded 7 patients in de CTS group with gestational diabetes, who were not indicated as diabetes patients in the previous analysis. In the revised version the CTS group and the control group only contains patients with type 2 DM. The new study population consists of 997 CTS patients and 594 controls.

Please explain why only patients who had NCS were included in the study. Did all of the patients with HNP have NCS?

The patients with an HNP didn’t have had NCS. We only included CTS patients who have had NCS because in the analysis we wanted to distinguish between patients who had NCS confirmed CTS and who had not. If we had included patients without NCS, we would of course not have known if their CTS would be NCS confirmed, which in our view would limit the strength of our analyses. Fortunately, the group of patients with CTS which could not be confirmed by NCS was very small so we did not performed subgroup analysis.

There is no "gold standard" for the diagnosis of CTS (line 64).

Aroori et al. (references number 1) described NCS in their review as the gold standard test for CTS. However, they also mentioned the false positive and false negative results. Therefore they referred to studies which suggest that NCS alone should not be used to diagnose. They described the combination of clinical symptoms and signs with electro-diagnostic findings as the most valid way of diagnosing CTS.

We removed ‘gold standard’ and changed the sentence about the diagnosis in the following: (page 3, line 58) "The combination of these clinical symptoms together with positive signs by physical examination and nerve conduction studies (NCS) is the most valid way of diagnosing CTS."

Please describe the reasons for excluding 468 CTS patients and 171 HNP patients. Which criteria were not met?

We have added a flowchart of the exclusion criteria to the tables en figures section of this manuscript.

Please explain why a random sample of controls wasn’t used?

We could not use a control group consisting of a random sample of patients because DM status and BMI data would then be missing for many patients in the control group. For most of the patients who are treated in outpatients clinic of our hospital it is unknown if they have a diagnosis of DM and the BMI is mostly not calculated for those patients. Therefore we selected only patients who have had a preoperative anaesthetic medical consultation. The goals of this consultation are to determine the risk to the patient of the proposed procedure and to minimize known risks. The BMI is always calculated during this consultation and patients are asked for their DM status. Furthermore, only operated HNP patients were chosen with the thought that HNP patients would be reasonably matched on age with the CTS group and because it is a frequently diagnosed disease which makes it possible to build a control group consisting of enough patients.

In order to clarify this topic in the manuscript, we added the following sentences to the material and methods section:
(page 4, line 96) “HNP patients were chosen assuming that HNP patients would be derived from about the same age category as the CTS group and because it is a frequently diagnosed disease which makes it possible to build a control group consisting of enough patients. Finally only operated patients were chosen because DM status and BMI data are known for the majority of operated patients in our hospital.”

Minor Essential Revisions
Consider "after adjusting for possible confounders" instead of "using more possible confounders" in line 33.

"and" in place of "en" in line 98

"individual" instead of "individually" in line 99.

"and" instead of "as" in line 167

Discretionary Revisions
In the discussion, you could expand further on which previous studies examined or controlled for these risk factors and whether or not this might have resulted in conclusions similar to the current study instead of just referring to the systematic review.

Thank you for the suggestion. We only referred to the systematic review because the included studies in this review did not describe in particular about the influence of BMI and age in a way that is has additional value for our manuscript.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being Published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer 2

Title: Diabetes is not a risk factor for the carpal tunnel syndrome

Version: 2 Date: 10 April 2014

Reviewer: Elisabeth Chroni

Reviewer’s report:

Major Compulsory Revisions

The authors of the submitted manuscript examined the relation between diabetes mellitus and carpal tunnel syndrome (CTS). The topic is clinically significant since CTS is the commonest mononeuropathy resulting in considerable morbidity and many work-loss days. The methodology used is appropriate and the discussion relevant to the manuscript’s aim. However, there are few issues that need clarification.

The reason for using a control group that was mismatched for sex, age and individuals’ number with the study group is unclear to me. It would be preferable (and less statistically complicated) to use a control group matched for sex and age at least.

The initial idea was to choose a control group matched for sex and age, which was randomly selected from all the patients who were treated in the hospital. However, we could not use this method because data on BMI and DM status would be missing for many patients. For most of the patients who are treated in outpatients clinic of our hospital it is unknown if they have a diagnosis of DM and the BMI is mostly not calculated for those patients in a way that is extractible from electronic records. Therefore we have chosen a control group consisting of patients who have had preoperatively consultation. Weight and length are (almost) always measured during this consultation and all patients are checked for co-morbidities like diabetes. Only operated HNP patients were chosen with the thought that HNP patients would as a group be matched reasonably well on age with the CTS group and because it is a frequently diagnosed disease which makes it possible to build a control group consisting of enough patients.

In order to clarify this topic in the manuscript, we added the following sentences to the material and methods section:

(page 4, line 96) “HNP patients were chosen assuming that HNP patients would be derived from about the same age category as the CTS group and because it is a frequently diagnosed disease which makes it possible to build a control group consisting of enough patients. Finally only operated patients were chosen because DM status and BMI data are known for the majority of operated patients in our hospital.”

The gold standard of electrophysiological examination for CTS is not mentioned. Did they include patients based only on clinical symptoms, without neurophysiological confirmation? (line 85). How one can be sure that the symptoms were actually due to CTS and not to other conditions (musculoskeletal disorders, radiculopathies)? Did the authors exclude patients with other neuropathies (i.e. alcohol abuse, or hypothyroidism)? What were the criteria used to recognize CTS superimposed on diabetic polyneuropathy?

We did include patient with CTS symptoms without neurophysiological confirmation (7.6%). However, the same results were obtained when only patients with CTS confirmed with NCS were included as mentioned in the result section. The CTS diagnosis was based on the
judgment of a neurologist or plastic surgeon which was written in the electronic patient record of the CTS patients complemented with the results of NCS.
We did not explicit exclude patients with other neuropathies and there were no specific criteria used to recognize CTS superimposed on diabetic polyneuropathy. However, we excluded all the patients whose CTS diagnoses was described as being doubtful in the patient record. In total, 256 patients with ‘no typical CTS symptoms’ were excluded from analysis.

It would be interested to know the result for DM type I and II separately. We totally agree with the authors that obesity which is a predisposing factor for CTS could be the underlying factor that connects DM type II with CTS. If this is the case, then only DM type I would not be related to CTS.

It would indeed be interesting. Unfortunately, there were only 10 patients with type 1 diabetes in de CTS and 0 patients with type 1 diabetes in the HNP group, so we were unable to analyze this. Reviewer one suggested to exclude the patients with T1DM. We have only included patients with T2DM in the revised version of the manuscript.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests

Reviewer 3

Title: Diabetes is not a risk factor for the carpal tunnel syndrome
Version: 2 Date: 8 May 2014
Reviewer: Jeferson Becker

Reviewer's report:

Firstly, there are studies that question DM as a risk factor (RF) for CTS (for example, Becker, 2002). This should be better addressed in the introduction.

We addressed more studies which investigated DM as a risk factor for CTS to the introduction (including the study from Becker et al.).

The biggest problem, however, is in the choice of control group. This one is inappropriate because HNP, especially lumbosacral, is associated with obesity and DM, and thus, this control group is not ideal for measuring risk factors for CTS. It would be more appropriate to compare with a control group without neuromuscular disorders and with a normal neurophysiological assessment, or alternatively, with diverse neuromuscular diseases, collected randomly and consecutively. Another possibility would be to say that DM is not a RF when compared with HNP, although this would weaken the strength of the study.

We fully agree that it would be better the choose a control group consisting of individuals without neuromuscular disorders or with diverse neuromuscular diseases. However, this was not possible for practical reasons. We needed data regarding BMI and DM and these data are scarcely available for a control group as you have proposed. Therefore we have chosen a control group consisting of patients who have had preoperatively consultation. Weight and
length are almost always measured during this consultation and all patients are checked for co-morbidities like diabetes.

Only operated HNP patients were chosen with the thought that HNP patients would as a group be matched reasonably well on age with the CTS group and because it is a frequently diagnosed disease which makes it possible to build a control group consisting of enough patients.

In our opinion the evidence showing that DM is associated with HNP is very limited and HNP being associated with BMI is in essence not a problem in order to answer our research question. However we do agree that there is some evidence about the relation between DM and HNP as also many diseases are more or less related with DM. Therefore we changed the limitation section in our abstract in the following:

"The choice to use surgery-treated HNP patients as a control population is a topic for debate. Smaller studies have described a relationship between DM and HNP, so although inconclusive, the prevalence of T2DM could be higher among these persons than in the general population."

Finally, I suggest other minor alterations:

- Line 66: adjust the prevalence for men and women and not just one number for both, since the female gender is an independent risk factor for CTS;

  We changed this sentence in the following:
  (page 8, line 190) “The prevalence of CTS in the general population is approximately 2.1% for men and 3.0% for women.”

- Line 98: correct 'CTS en HNP';

  Changed.

- Line 136: better describe the ages, not putting only the means and confidence intervals;

  We added the mean age for both groups to the result section of our manuscript. In our opinion it has no additional value to describe the ages in more detail. We would like to receive some suggestions if you want to have an extensive explanation of the ages.

  We added the following sentence to the result section:
  (page 7, line 155) “The mean age was 55.7 (±15.2) years in the CTS group and 49.3 (±13.0) years in the control group (p < 0.001).”

- Line 138: ‘was significantly higher’

  Changed.

Comments from the Associate Editor (Mauro Mondelli)

Dear authors,

your study is interesting because it shows that diabetes is not a risk factor of CTS. This claim contradicts what reported so far in the literature with the exception of the study by de Krom et al.

I read the referees remarks and I fully agree with them.
I have some other questions and criticisms.
1) As the referee no.1 already requested, the authors should provide more information on the recruitment site (Isala clinics, secondary care setting) and on the population at risk (were the patients resident in the city of Zwolle and/or in three regions of Overijssel province or in other Dutch provinces?).

What is the estimated number of diabetic patients and patients with CTS in the population from which the cases and controls come from? What is the percentage of these patients with diabetes and with CTS that the authors think to capture?

As previously mentioned in the reply to reviewer 1, we added more information on the recruitment site and population at risk to the method section:

(page 4, line 78) “This study was conducted at the Isala, a general hospital with a catchment area of 800,000 inhabitants in the North East of the Netherlands. All patients with severe symptoms of CTS or with symptoms which could not be treated by a general practitioner with a conservative approach (i.e. watchful waiting, a brace or corticosteroid injections) and who were referred to the outpatient clinic of the Isala between January 2011 and July 2012 were identified.”

All patients in our study were residents of Zwolle or residents of cities nearby Zwolle. The population of the Zwolle region consists of almost 310,000 individuals and almost 15,000 of them have T2DM. Our study includes 158 diabetes patients, so we captured only 1% of this diabetes population.

According to atroshi et al., the prevalence of CTS is 2.7% in the general population so the estimated number of CTS patients in the Zwolle region will be 8100. Our studies includes 997 Patients with CTS, so we captured 12% of the CTS patients. We captured only a small amount of the CTS patients because of the fact that most of the patients with CTS are treated by a general practitioner.

2) What does Diagnosis-treatment-combination codes? mean? Have the authors used the international classification of diagnosis (ICD)? If so, what codes did the authors use? If not, was there Isala Clinics coding of admitted patients and how is it built?

In the Netherlands, physicians register and declare the delivered care using Diagnosis Treatment Combinations-codes (DTC-codes). Each DTC code contains information about the specialization of the treating physician, the patient’s diagnosis and the type of treatment provided and each combination of a diagnosis and treatment has a unique DBC code.

We have explained the Diagnosis-treatment-combination codes in more detail in the method section:

(page 5, line 105) “Patients, both CTS cases and the HNP controls, were identified using diagnosis-treatment-combination (DTC) codes, which are used in the Netherlands for both hospital registration and health insurance declaration purposes. Each DTC code contains information about the specialization of the treating physician, the patient’s diagnosis and the type of treatment provided. CTS patients were identified using DTC codes 0304.350, 0304.351 and 0330.0801 and HNP patients using the DTC codes 0308.2530, 0308.2550, 0308.2555.”

We did not use the international classification of diagnosis. We identified the patients using the DTC codes and subsequently we checked all the patients records to verify the CTS and HNP diagnoses.
3) Were the enrolled patients outpatients and inpatients?

All the patients were outpatients. All the CTS patients were referred to the department of neurology or plastic surgery by their general practitioner. All the HNP patients were referred to the department of neurosurgery by a neurologist.

We have added ‘outpatient clinic’ to the study and design part of the material and methods.

4) Were NCVs performed with the same methods (what were they?) and with the same equipment?

The nerve conduction studies were performed with the same methods and with the same equipment at the department of neurology of the Isala.

We have described the NCS in more detail:
(page 4, line 86) “NCS were executed by a neurologist and consisted of 1 motor and 2 sensible conduction tests. A comparison was made of the distal motor latencies from the median nerve to the second lumbrical and from the ulnar nerve to the second interosseous muscle with equal distances. Furthermore, a comparison was made of the sensory conduction of the median nerve with the ulnar nerve between wrist and digit 4 and of the sensory conduction of the median with the radial nerve between wrist and thumb. If two of three tests were abnormal, the diagnosis of CTS was electrophysiological confirmed.

5) Why did the authors choose only patients with HNP as controls? The sentence at page 7 line 170? the choice for controls? is arbitrary? is unacceptable, because the authors think they can extend the results in the general population (Page 4, line 87). Actually the authors can compare only patients with CTS with those with HNP.

The choice for HNP patients was mostly based on practical reasons which are previously mentioned in our replies to reviewer 1, 2 and 3.

Nevertheless, we acknowledge that the choice of HNP patients as controls has its limitations. Strictly said, we can only compare patients with CTS with those with HNP. Evidence, that diabetes is related or unrelated with HNP is very scarce and inconclusive. We agree that the generalisability to the general population is limited by the choice of the control group.

We changed the limitation section of the discussion in the following:
(page 8, line 190) “The choice to use surgery-treated HNP patients as a control population is a topic for debate. Smaller studies have described a relationship between DM and HNP, so although inconclusive, the prevalence of T2DM could be higher among these persons than in the general population.”

6) I have three little questions on HNP patients: Why did the authors choose only operated patients and not all the patients diagnosed with disc herniation? Had the patients the herniated disc at the cervical or lumbar spine level? How many HNP patients were excluded because they also had CTS (page 4, line 91)?

We have chosen only operated patients because we needed information on diabetes and BMI and therefore we could only include patients who had received preoperatively consultation as mentioned in the reaction to the first question of reviewer 2.
We have added the following sentence to the result section of the manuscript:

(page 7, line 160) “Four hundred twenty-one patients in the control group had a herniated disc at the lumbar spine level and 173 patients had a herniated disc at the cervical level.”

36 HNP patients were excluded because they had CTS as well. A flowchart of the exclusion criteria is depicted in figure 1.

7) The sentences at lines 163-9 are unclear. I think that the authors want to say that one of the strengths of the study was the site enrolment (primary and secondary care setting at the same time). If so, they should explain this.

Unfortunately this study did not cover primary and secondary care at the same time. In other words, the generalizability of this study is limited to secondary care because of the fact that only patients with CTS who were treated in secondary care were included. We tried to clarify our point in the text:

(page 8, line 186) “Since data regarding T2DM from both primary and secondary care was used, and the prevalence of T2DM and complications is higher in secondary care, the setting of our study could therefore strengthen our findings. However, it also limits the generalizability to secondary care.”

8) When the authors cite the study of de Krom et al. (line 178), they should emphasize scientific rigor in the sample selection (age and sex-stratified random sample from the population register of Maastricht and some surrounding villages). Selection bias is minimized with that enrolment method.

Thank you for the suggestion. We added the following sentence to the discussion.

(page 8, line 198) “Similar to our results, a study among 156 CTS patients and 473 age and sex matched controls derived from a Dutch population register could not find a relation between DM and CTS.”

9) The bibliographic search is largely incomplete, the authors should cite and briefly comment the following papers:

Thank you for your research in the literature. We added 6 of the suggested 7 references to the revised version of the manuscript.


g) Coggon D et al. Differences in risk factors for neurophysiologically confirmed carpal tunnel syndrome and illness with similar symptoms but normal median nerve function: a case-control study. BMC Musculoskelet Disord. 2013 Aug 15;14:240.