Author’s response to reviews

Title: Risk factors for operated carpal tunnel syndrome A multicenter population-based case-control study

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Version: 2 Date: 19 March 2009

Author’s response to reviews: see over
March 19, 2009

Dear Dr. Norton,

MS: 1853933867235803
Risk factors for operated carpal tunnel syndrome. A multicenter population-based case-control study (Mattioli et al).

Thank you for reviewing this submission. Please find attached our careful revision based on the comments of your three reviewers. Our point-by-point replies to each reviewer are listed below.

Please note that this resubmission includes four Additional files (previously marked Table A to D). Furthermore, in response to questions from reviewers 2 and 3 we now include a new Table (Table 7) in the Discussion providing figures comparing sex-specific incidence rates of surgically-treated CTS and clinically/instrumentally diagnosed CTS in the province of Siena.

I look forward to hearing from you.

Sincerely yours

Gianpiero Mancini, MD

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Reviewer's report

Title: Risk factors for operated carpal tunnel syndrome A multicenter population-based case-control study
Version: 1 Date: 15 December 2008
Reviewer: Frank Burke

Reviewer's report:
The paper is of some interest but perhaps it would have been better to simply enrol females and enrol a far larger number. The authors have tried to analyse several subgroups and the numbers in each group inevitably end up very low. A 74% response rate is also a concern. I am not sure the paper offers so much that is new but readers will be interested in its conclusions.

Reply: The study was designed to investigate risk factors in both men and women. We did discuss the concern about response and its implications in the Study limitations subsection: “In view of the good but not ideal response (74%) to the full questionnaire among potential controls, non-response bias may have influenced the main findings regarding socio-occupational status. Although this factor could have led to a slight overestimate of the risks associated with blue-collar/housewife status, it seems unlikely that the 7-fold excess risk could be mainly attributable to blue-collar/housewife non-responders among controls.” It’s also perhaps worth remarking that comparatively few population-based case-control studies manage to achieve a higher response among controls. We are glad that the reviewer recognizes that the implications of the results of the study are of interest.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report

Title: Risk factors for operated carpal tunnel syndrome A multicenter population-based case-control study
Version: 1 Date: 1 January 2009

Reviewer: ALFRED MD FRANZBLAU

Reviewer's report:

Title: Risk factors for operated carpal tunnel syndrome: A multicenter population-based case-control study
Authors: Stefano Mattioli, Alberto Baldasseroni, Massimo Bovenzi, Stefania Curti, Robin M T Cooke, Giuseppe Campo, Pietro G Barbieri, Rinaldo Ghersi, Marco Broccoli, Maria Pia Cancellieri, Anna Maria Colao, Marco dell'Omo, Pirous Fateh-Moghadam, Flavia Franceschini, Serenella Fucksia, Paolo Galli, Fabriziomaria Gobba, Roberto Lucchini, Anna Mandes, Teresa Marras, Carla Sgarrella, Stefano Borghesi, Mauro Fierro, Francesca Zanardi, Gianpiero Mancini and Francesco S Violante

Major compulsory revisions:
This study focuses on identifying risk factors for carpal tunnel syndrome (CTS) based on analyses of surgically treated patients from 13 regions in central and northern Italy. The sampling frame comprised all residents in these regions in the year 2001 who had been admitted to hospital with CTS as the principal diagnosis (ICD-9 code 354.0) and who had undergone surgical treatment for CTS (DRG code 06). Each center identified 20 cases and 40 controls to be included in the study. The goal was to perform a population-based case-control study of surgically treated CTS to identify both occupational and non-occupational risk factors for CTS. This is a very important issue since, as noted by the authors, almost all studies of CTS have focused on either occupational or non-occupational factors, or have not been designed in a manner that allows extrapolation of results to the general population.
We thank the reviewer for the careful critical appraisal and his appreciation of the relevance of the issues addressed in the study.

Question: What about patients with CTS who do not undergo surgical treatment? What fraction of patients diagnosed with CTS in Italy do not have surgery? In the United States a rather large fraction of patients diagnosed with CTS do not undergo surgical release. How might such patients differ from those who have surgery? This is a particularly important question in the current study, which, like many previous studies, found that blue collar workers were at higher risk compared to white collar workers. If white collar workers are not ‘occupationally disadvantaged’ by CTS to the same extent as blue collar workers, then a study based only on surgically treated cases would be biased.

Reply: The reviewer makes some important points, which we had largely tried to address in the second paragraph of the Study Limitations subsection.
We have inserted a new Table (in the Discussion section) providing some indications regarding the proportion of Italian patients diagnosed with CTS who do not have surgery. Table 7 juxtaposes from a study by Mondelli et al [ref 42; Neurology 2002;58:289-94] on incidence of electromyographically confirmed symptomatic CTS in Siena alongside comparable data extracted from our own previous work on incidence of surgically-treated disease [ref 43; Mattioli et al]. As we noted in the Discussion of ref 43, the proportion of conservative treatment among electromyographically diagnosed patients in
Siena seems to be 50% or more, a figure “broadly in line with a comparison of neurophysiologically confirmed and surgically treated CTS rates in East Kent (England) [Bland et al, Neurol Neurosurg Psychiatry 2003;74:1674-1679], but somewhat higher than the proportion (31%) of surgically treated cases of CTS reported in a recent study of incidence compressive neuropathies in UK general practices [Latinovic et al, J Neurol Neurosurg Psychiatry 2006;77:263-265]. It should also be remembered that the prevalence of symptomatic cases of CTS in the general population appears to be considerably higher than that of diagnosed cases [Atroshi et al, JAMA 1999, 282:153-158].”

To gain indications on the different characteristics patients who do and do not undergo surgical treatment in Italy, we referred to a paper [now ref 44] by Mondelli et al (Eur J Neurol 2005;12:976-83) which contains pertinent data regarding the general population of Siena in Tuscany. Although the authors did not conduct formal statistical comparisons, eyeballing Tables 1 and 2 suggests that surgically treated patients tended to experience more severe symptoms over a longer period of time and to have a more marked electrophysiological profile. If we make the fairly plausible assumption that the data from Siena can be broadly generalized to other parts of Italy, it would seem that surgical treatment may be a marker of more clinically and neurologically severe disease.

Interestingly, the data reported by Mondelli et al do not seem to corroborate the reviewer’s justified concern that occupational need for surgical treatment among blue-collar workers may have biased our results towards overestimates of the risks associated with manual jobs. Indeed, the observation that patients who were not referred for surgical treatment seemed to have a slightly lower level of education suggests that any bias of this sort might have led to a slight underestimate. Nevertheless, we do feel that it is correct to remark on this issue as a potential study limitation.

Based on the reviewer’s queries, we have now largely rewritten the 2nd paragraph of the Study Limitations subsection: “The risk estimates reported in the present study regard surgically-treated CTS and cannot automatically be extended to all clinically relevant cases of CTS. In the general population of Siena (Tuscany) [42,43], surgical treatment seems to be performed in no more than about half the patients with an electromyographically confirmed diagnosis of symptomatic CTS (Table 7). In Siena at least, surgically treated patients [44] seem to have a more severe clinical and electrophysiological profile than untreated patients. In other respects, however, the characteristics of the two groups [44] appear broadly similar apart from a slightly lower level of education among the patients not submitted to surgical treatment. This knowledge seems to attenuate the legitimate concern that blue-collar workers, housewives and mothers of several children might have greater incentives to undergo surgical decompression of the median nerve in order to remain fit for essential manual activities (whereas male white-collar workers might be better placed to avoid particular tasks and postpone or avoid surgical treatment). We think that use of ‘surgically-treated CTS’ as a case definition may provide (in Italy at least) a heuristic tool to help spotlight more clinically severe and socially relevant disease.”

**Question:** Twenty cases and 40 controls were selected from the records at each center. Presumably the selection process involved some sort of random selection so as to maximize the likelihood that the selected cases and controls would be representative of the underlying population of eligible cases and controls at each center. Exactly how were cases and controls selected in order to ensure randomness?

**Reply:** In the Methods section, we have now specified that “For both cases and controls, randomization was independently conducted by local Epidemiology Units”. The study protocol required that each center ask the Epidemiology Unit attached to their Local Health Authority to conduct the randomization. Each Epidemiology Unit was then free to select its preferred randomization method (as long as it was a valid and recognized one for use for extraction of cases and controls from the general population). This approach was adopted to ensure the validity of the randomization while avoiding unnecessary bureaucracy.
**Question:** It is asserted that this study is “population based”, and this is, in fact, one of the potential strengths of the study. The number of cases and controls selected from each of the 13 centers was the same, but we don’t know the underlying number of eligible cases and controls for each center. The assumption appears to be that the latter numbers are roughly the same, in which case the implicit weights assigned to cases and controls from different centers is roughly equal and so no formal adjustments or ‘weights’ are needed in analyses to make the results representative of the underlying populations. However, if the number of eligible cases and controls differed substantially by center, then the true relative weights of the selected cases and controls would be unequal between centers, and this should have been adjusted for in models. This becomes particularly important in making calculations of population attributable risk (PAR). Furthermore, if the population rates of surgical CTS differed much by center, this may suggest a number of important issues, including: 1) the underlying risk factors for surgical CTS may have varied across centers; or 2) the diagnostic and/or treatment criteria for CTS may have varied across centers. The authors appear to confirm that the first item may hold true (see Discussion: “many industrial job titles were poorly represented due to regional employment characteristics”). This study appears to not have been set up as a prospective trial with uniform diagnostic and treatment criteria for all participating centers and so the latter issue is of particular concern and needs to be addressed.

**Reply:** The reviewer is of course right—especially since the cases were drawn from routine health service records. The analyses reported in the original submission were not adjusted for center due to issues in early models regarding collinearity with BMI. However, on rerunning the final models, we notice that this problem no longer subsists. Therefore, we now present results after adjusting for center; the main results remain substantially unchanged. Of course, this procedure cannot resolve the study limitation regarding the relatively poor representation of many industrial job titles (hindering recognition of genuinely at-risk activities). We thank the reviewer for prompting us to review this question.

It is stated that at the time of the study almost all CTS release surgeries were performed “on hospital premises after diagnostic confirmation by nerve conduction studies”.

**Question:** In Italy are all patients who have surgery for CTS “admitted” to a hospital? In the US almost no one is ‘admitted’ to hospital (i.e., spend at least one night in the hospital) for CTS release surgery – this is considered an ‘outpatient’ procedure – even though many CTS surgeries are performed on hospital premises. Many surgeries are also performed in non-hospital settings, such as doctors’ offices or outpatient surgical centers. Does this apply in Italy? This question may revolve on the meaning of the words ‘admitted to a hospital’, and requires clarification. Also, use of nerve conduction tests to confirm the diagnosis of CTS is a strength of the study. However, as mentioned above, there is no mention of uniform diagnostic criteria, particularly electrodiagnostic criteria, that may have been applied in all 13 centers.

**Reply:** In Italy, any patient undergoing surgical treatment—even on an outpatient basis—has to be formally “admitted” to hospital [in Italian, “ricoverato”] even if only for a few hours. Furthermore, at the time of the study, regional regulations throughout Italy required that carpal tunnel release operations must be performed on hospital premises (of note, some regions have now relaxed this rule). We have now specified these points more clearly in the Methods section: “At the time of the study, Italian regulations required that carpal tunnel release operations be conducted only on hospital premises. All patients undergoing this treatment—even on an outpatient basis—had to be formally admitted to hospital (even if only for a few hours). Furthermore, diagnostic confirmation by nerve conduction studies was generally considered a prerequisite for carpal tunnel release.” Please note that even in the absence of uniform diagnostic criteria, it was common practice throughout Italy to perform
carpal tunnel release only after diagnostic confirmation of CTS based on nerve conduction studies. The risk of legal consequences in the event of postoperative side effects would have been a very strong deterrent to referral to surgery in the absence of nerve conduction studies.

Selection of controls was based on random sampling from the national health service registries covering each of the thirteen administrative centers included in the study. Control subjects who had received surgical treatment for CTS were excluded.

**Question:** What about controls who may have been diagnosed with CTS but did not have surgical treatment for CTS? Could such potential controls be identified from the administrative data (or the questionnaire), and, if so, were they excluded?

**Reply:** No, the questionnaire did not attempt to elicit information on symptomatic CTS and there was no reliable way of gaining information from administrative data. Likely presence of a few controls with symptomatic CTS would presumably have led to slight underestimates of the recorded OR. However, we do not think that this factor would greatly affect the main results of the study.

In the Results section, under ‘Response’, it is stated that for only one case was the questionnaire filled in by the next of kin.

**Question:** For how many controls was the questionnaire filled in by the next of kin? Responses from next of kin probably should be excluded from analyses for both cases and controls.

As we have now additionally specified in the Results section, none of the ‘control’ questionnaires was filled in by a next of kin. Therefore, only one proxy response entered the analysis. Even though next-of-kin responses regarding habitual physical activity may be a little less reliable than proxy information on smoking and drinking (Graham and Jackson, J Epidemiol Biostat 2000;5:255-65), we do not think that this issue should be a concern in this numerical context. We have therefore retained the single proxy response in the final analysis.

In Table 1, which includes non-retired men and women combined, the cases = 191, and the controls = 286. The numbers shown in Table 2 appear to match these overall numbers for non-retired men and women, and also show the genders separately: female cases = 163, female controls = 238; male cases = 28, male controls = 48. In Supplemental Table C, which reports results for non-retired women, the number of cases = 169 (last 10 years), and cases = 184 (lifetime), and the controls = 249 and 285, respectively.

**Question:** The number of female cases and controls presented in Tables 1, 2, & C appear to differ, and it is difficult to reconcile the differences. How come the number of non-retired female cases is listed as 163 in Table 2, but 169 and 184 in Supplemental Table C? Similarly, the number of non-retired female controls also varies: Table 2 = 238; Supplemental Table C = 249 (last 10 years) and 285 (lifetime)?

**Reply:** This apparent discrepancy derives from the different numbers of subjects satisfying the three different definitions of “prevalent” job titles. More people will satisfy a definition based on lifetime prevalence than one based on “prevalent in the last 10 years” or (as in the main analysis) “prevalent in the last 2 years”. We have now added a footnote to Additional file 3 (previously Table C) explaining why the totals do not correspond.

**Minor Essential Revision:**
In the Methods section, under Statistical Analysis, a number of factors are listed as categorical variables including “familiarity”.

**Question:** Does “familiarity” refer to ‘family history of CTS’? It might be better to use the latter terminology.
Reply: Yes, as rightly suggested we have now replaced “familiarity” with “family history of CTS”.

In the Discussion it is mentioned that “Another possible association which needs to be tested in larger studies regards surgical treatment for CTS in siblings. This putative risk factor could be attributed to genetic and/or familial environmental factors.” Presumably, the authors are referring to the high odds ratio for CTS in a sibling as a risk factor for CTS in the study population (unadjusted OR = 8.1, adjusted OR = 5.7; see Table 1). This is an important finding, and possibly should be stated more explicitly.

Question: The twin study by Hakim et al. (2002) is cited in the Background. Hakim et al. found that inherited factors explained almost 50% of the variance in a classical twin study analysis. The finding in the current study that CTS in a sibling was an important risk factor is therefore notable. The study by Hakim et al should also be cited and mentioned here in the Discussion in conjunction with discussion of the sibling results.

Reply: We thank the reviewer for drawing attention to the pertinence of the twin study by Hakim et al in this context. We have now added a sentence to the Discussion remarking that “…the finding of an almost 7-fold excess risk in subjects with an affected sibling is particularly interesting in the light of a study of female twins which suggested that up to half the risk of CTS in women may be genetically determined [7].”

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report

Title: Risk factors for operated carpal tunnel syndrome A multicenter population-based case-control study  
Version: 1 Date: 2 February 2009

Reviewer: Andrew CF Hui

Reviewer's report:  
- Major Compulsory Revisions

The database was a surgical one; how representative was this of CTS in general – what are the criteria for decompression? does it mean the same as severe CTS?

Reply: As also explained in our reply to the review by Professor Franzblau [see above], even in the absence of uniform diagnostic criteria, it was common practice throughout Italy during the study period to perform carpal tunnel release only after diagnostic confirmation of CTS based on nerve conduction studies. The risk of legal consequences in the event of postoperative side effects would have been a very strong deterrent to referral to surgery in the absence of nerve conduction studies. To gain indications on the different characteristics patients who do and do not undergo surgical treatment in Italy, we referred to a paper [now ref 44] by Mondelli et al (Eur J Neurol 2005;12:976-83) which contains pertinent data regarding the general population of Siena in Tuscany. Although the authors did not conduct formal statistical comparisons, eyeballing Tables 1 and 2 suggests that surgically treated patients tended to experience more severe symptoms over a longer period of time and to have a more marked electrophysiological profile. If we make the fairly plausible assumption that the data from Siena can be broadly generalized to other parts of Italy, it would seem that surgical treatment may be a marker of more clinically and neurologically severe disease.

We did address this question in the Study Limitations subsection, which we have now expanded with the inclusion of a further Table. This paragraph now reads: “The risk estimates reported in the present study regard surgically-treated CTS and cannot automatically be extended to all clinically relevant cases of CTS. In the general population of Siena (Tuscany) [42,43], surgical treatment seems to be performed in no more than about half the patients with an electromyographically confirmed diagnosis of symptomatic CTS (Table 7). In Siena at least, surgically treated patients [44] seem to have a more severe clinical and electrophysiological profile than untreated patients. In other respects, however, the characteristics of the two groups [44] appear broadly similar apart from a slightly lower level of education among the patients not submitted to surgical treatment. This knowledge seems to attenuate the legitimate concern that blue-collar workers, housewives and mothers of several children might have greater incentives to undergo surgical decompression of the median nerve in order to remain fit for essential manual activities (whereas male white-collar workers might be better placed to avoid particular tasks and postpone or avoid surgical treatment). We think that use of ‘surgically-treated CTS’ as a case definition may provide (in Italy at least) a heuristic tool to help spotlight more clinically severe and socially relevant disease.”

The findings are undermined by the small number of patients that were studied (considering also this is a condition that affects 5% of the population and this collaboration involved 13 centres). In some categories there were as few as n=3 (white collar men) or 5 (the number of metal workers); this is reflected in the large CI (eg 4.7 –122) for some variables. I think that looking at over 10 variables with such a small sample size is statistically unsound.

Reply: We fully agree with the reviewer that overinterpretation of OR deriving from small numbers must be avoided and we were rather careful about this in the Discussion section. Indeed, we stressed
the fact that many job titles were poorly represented in this study due to regional employment characteristics. Nevertheless, we think that the results the reviewer refers to should all be reported in the Table, especially in view of their possible relevance for systematic reviews or meta-analysis. Please also note that we have now also adjusted for center in the analysis.

**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