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: 4 Date: 24 July 2009

Author's response to reviews: see over
16 July 2009

Dear Dr Titmus,

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

Thank you for reviewing our resubmission. Please find attached our careful final revision based on the comments of your two reviewers, including the member of the editorial board. We would like to thank both of them and indeed your entire team. Our point-by-point replies to each reviewer are listed below.

Please note that we did send you an email on July 2nd containing a couple of queries intended for Jens Peter Bonde (the member of the editorial board), requesting clarification of his briefly stated concerns regarding selection bias (“preferential selection depending on manual labour”) and “how the reference group was established”.

Since we have received no reply to this request, we think it is reasonable to assume that Dr Bonde’s concerns corresponded to those briefly outlined in our email: ie the occupational characteristics of the general population in the areas under study and whether the choice of the white-collar reference group was in some way arbitrary.

We have directly addressed these concerns in the latest revision of the Discussion section and in our point-by-point replies. We appreciate Dr Bonde’s concern that the limitations of the study must be spelled out clearly and we have endeavored to do this not only in the Study Limitations subsection but also, implicitly, in the rest of the Discussion. We were particularly careful to avoid overinterpretation and to draw appropriate conclusions. In particular, we think the present work really does underline the relevance of biomechanical exposures encountered in some industrial and non-industrial manual work. We have underlined the point that this interpretation in no way plays down the risks that have been shown elsewhere to be associated with certain white-collar jobs that involve intensive mouse and keyboard work.

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: 2 Date: 22 April 2009

Reviewer: Andrew CF Hui

Reviewer's report:
Under study limitations in the discussion section, the small sample size is commented on.
Yes, we have inserted an entirely new paragraph at the start of the study limitations subsection highlighting some issues which seem to us to be particularly pertinent: “It should be underlined that the sample size was not large enough to address many of the study objectives with confidence. The suggestive findings emerging from the present work require confirmation in appropriately sized studies, and also in geographic settings with different employment characteristics. Indeed, as noted above, many relevant job titles were either poorly represented or absent in our limited sample. For instance, the very high risks recorded for the broad blue-collar category may partially be attributed to the relative absence of intensive keyboard/mouse users such as data processors in the study sample.”

An alternative could be found for "being tall" - could we replace that with "height" and qualifying by saying that "taller individuals are less likely to suffer from CTS" etc.
Thank you for drawing attention to this stylistic point. In the Discussion section, we have broadly followed your suggestion. In the Results and Abstract, where we need to refer to the variable itself, we now prefer to talk about “being relatively tall.” We think this phrase is technically correct because identification of the two groups of interest was based on the upper tertile of the women and men controls (and the cut-offs used were not actually particularly high in absolute terms).

Thank you for making these helpful suggestions.
Reviewer's report

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

Version: 2 Date: 30 June 2009

Reviewer: Jens Peter Bonde

Reviewer's report:
In considering the revised paper and the reviews I am in favour of publication in spite of the obvious limitations, first of all limited study size (given the study objectives), uncertainties with respect to preferential selection depending on manual labour and with respect to how the reference group was established. It is a little strange that the risk is highly increased in all types of blue collar work and even among nurses. If the decision is to publish I would suggest that the limitations are reflected to a much higher degree in the conclusion.

We would like to thank you for the considerations and queries.

We have reinforced the Study Limitations subsection and added a final rider to the Conclusions: “If confirmed in larger studies, such considerations could be pertinent for prevention of socially/clinically relevant morbidity, and also for adjudication of workers’ compensation insurance claims.”

To emphasize the point about study size we have now inserted a paragraph at the start of the Study Limitations subsection highlighting this and other issues raised by the reviewer which seem to us to be particularly pertinent. The opening sentence of this paragraph reads: “It should be underlined that the sample size was not large enough to address many of the study objectives with confidence.”

We are not sure exactly what the uncertainties are about “preferential selection based on manual labour”. Since this was a population based study in several centers, the selection of case/controls should basically reflect (leaving aside considerations regarding play of chance and the small study) the characteristics of the general population in the areas under study. The particular employment characteristics in those geographical settings may raise selection bias considerations, and it is this issue we think the reviewer may be referring to. We already pointed out to reader that the preponderance of clerks in the white-collar group (reference category) and the lack of known at-risk non-manual job titles means that the study is not informative about the risks associated with jobs such as data processing. We have now expanded these concepts and their implications in the Discussion section: “… our findings must be interpreted in the context of the employment characteristics of the general population in the various centers. In particular, our reference category of women white-collar workers mainly comprised clerks who appeared to have little biomechanical exposure. It should be underlined that this study does not provide information regarding the highly relevant occupational category of data processors [29], who were poorly represented in the general population of the areas under study. Moreover, many industrial job titles were poorly represented due to regional employment characteristics…”.

We have also now drawn readers’ attention to the issue at the start of the Study Limitations subsection directly after the point about the small sample size: “The suggestive findings emerging from the present work require confirmation in appropriately sized studies, and also in geographic settings with different employment characteristics. Indeed, as noted above, many relevant job titles were either poorly represented or absent in our limited sample. For instance, the very high
risks recorded for the broad blue-collar category may partially be attributed to the relative absence of intensive keyboard/mouse users such as data processors in the study sample.”

As we already pointed out in the last paragraph of the Study Limitations subsection, it is also possible that the high OR for manual job titles may be partially attributable to the case definition of ‘operated’ CTS, since manual workers and housewives may conceivably reach surgical treatment more readily than office workers.

We agree that the category of nurses and paramedical workers does deserve special comment, especially since the 8-fold excess risk does seem remarkably high. We have now inserted the following comment on page 17: “The high OR recorded for nurses and paramedical workers could be attributable to several factors in addition to biomechanical risk factors, including possible facilitated access to surgical treatment for hospital workers. Nurse anesthetists are thought to be especially exposed to risk factors for CTS [35], but we have no way of knowing whether any or how many of the cases in the present study had this specific job title.”

We think that the query about “how the reference group was established” refers to the choice of white-collar workers as a reference category for the socio-occupational analysis. As discussed above – and in the revised Discussion section – we acknowledge that the particular composition of the white-collar workforce in the areas under study probably affects the magnitude of the risks associated with manual work in the present study.

We hope that we have addressed appropriately the issues you wished to raise.

UPDATE - 24 July:

Since making these revisions, we have received the clarification we requested from Professor Bonde regarding two of the points. We would like to thank Professor Bonde for his kind reply and to address these two points further in the light of his explanations.

1. Preferential selection related to labour: Employees with CTS may consult a medical doctor earlier and more often if they have manual work that elicit pain than workers without manual work. Thus seeking medical treatment may be dependent on a blue or white collar worker and result in selection bias in the recruitment phase of the study. In that case the results indicate more ‘troubles’ due to CTS among blue collar workers but not necessarily a higher occurrence of the disorder. The unspecificity of the findings - higher risk in most blue collar occupations rather than in particular jobs with exposures that are supposed to be strenuous to the hand-forearm - points to this interpretation.

We do accept the relevance of the forms of selection bias outlined by Professor Bonde (and already largely acknowledged in the Discussion) and accept the possibility that they may have biased the results in the direction of manual work. As we stated in 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) [22,44], 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 [45] seem to have a more severe clinical and electrophysiological profile
than untreated patients. In other respects, however, the characteristics of the two groups [45] 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.”

We have now added two closing sentences to highlight Professor Bonde’s specific concern: “Nevertheless, it must be stressed that a case definition of “surgically-treated CTS” will presumably lead to identification of risk factors for having “CTS-related troubles” severe enough to warrant surgery (rather than just experiencing the disease itself). The higher risks recorded for manual workers could at least partially stem from this consideration”.

2. Reference group: I had difficulties to understand exactly how the reference group was established and only ask for a more comprehensive description of matching procedures.

Yes, I’m afraid we misinterpreted this question in our original point-by-point reply above.

In response to the reviewer’s request, we have now added more information (underlined) in the Methods section to specify the frequency matching criteria: “Each center received standardized instructions (from S.M. and A.B.) for frequency matching criteria, based on reported age-sex-specific rates of hospitalization for CTS [21] in conjunction with a database regarding incidence of surgically treated CTS in the general population of seven Italian Regions [22]. In particular, each Epidemiology Unit randomly drew 40 controls (32 women, 8 men) in eight age-sex categories (18-34 yr: 4 women, 0 men; 35-44 yr: 6 women, 2 men; 45-54 yr: 14 women, 2 men; 55-65 yr: 8 women, 4 men).”

As we replied to Professor Franzblau in our point-by-point replies for the first resubmission, “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).”

We believe it is reasonable to assume that dedicated Epidemiology Units can be trusted to implement received randomization techniques appropriately.