**Author's response to reviews**

**Title:** Subgroup analyses on return to work in sick-listed employees with low back pain in a randomised trial comparing brief and multidisciplinary intervention.

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**Author's response to reviews:** see over
Hereby, we resubmit our paper previously entitled "Interaction effects of multidisciplinary intervention and workplace factors on return to work in sick-listed employees with low back pain in a randomised comparative trial"

Change of title was suggested by one of the referees, Eva Skillgate. Accordingly, we have rephrased the title as follows:
“Subgroup analyses on return to work in sick-listed employees with low back pain in a randomised trial comparing brief and multidisciplinary intervention.”

We greatly acknowledge the critical points and comments of the referees. The manuscript has now been changed in accordance. For more detailed answer, please see below. In the revised manuscript the paragraphs, which are new or considerably revised, are underlined. Underlining can easily be removed by “not accepting changes”.

The study was carried out in compliance with the Helsinki Declaration, but as originally stated in the ‘Methods’ section, the local ethics committee did not find it necessary to evaluate this. A letter from the committee confirming this statement is attached.

In 2004 a trial registration number was not required, and we were not aware of this issue later on. Now, we have registered the trial and the trial’s Trial Registration Number is written in the Methods section.

The manuscript has been revised to improve the English language style. These corrections have not been explicitly marked in the manuscript.

Yours sincerely

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Response to reviewer: Ivan Steenstra

We greatly acknowledge the critical points and comments of the referees. The manuscript has now been changed in accordance. For more detailed answer, please see below. In the revised manuscript the paragraphs, which are new or considerably revised, are underlined. Underlining can easily be removed by “not accepting changes”.

1.

We have rephrased objectives in the Introduction and added hypotheses:
“We hypothesized that particular subgroups defined by work-related factors would return earlier to work by a multidisciplinary than by a brief intervention, if these work-related factors could be expected to influence the RTW process. “

2 and 3.

Plausibility: We focused on work-related factors, because the relationship between a sick-listed employee and the workplace may be very emotional, and therefore may require an independent person to negotiate. An independent person was available for the patient in the multidisciplinary, not in the brief intervention.

In the Introduction we have written:
“Multidisciplinary interventions typically rely on tailor-made “treatments” to facilitate RTW, which implies that job modifications or other RTW facilitation measures are only initiated if they are necessary. They often include efforts directed towards changing job demands, job control, work organisation or towards increasing support. This requires close collaboration between workplace stakeholders, the sick-listed employee, members of the multidisciplinary team and - in the Danish context - also the social service centre responsible for sick leave reimbursement. However, if the employee and the workplace stakeholders agree on job modifications or other arrangements without the involvement of external stakeholders, the multidisciplinary intervention teams will not be involved. It is therefore relevant to study if self-reported work-related factors may be used to predict if the RTW process would benefit from intervention by professionals in the fields of occupational and social factors.”

In the Discussion, page 17 the following paragraph was included:
“However, it should also be considered whether these associations were, indeed, plausible; that is, we must ask ourselves whether the interventions could be expected to show different effects in these subgroups. Experts in occupational and social factors were only involved in the multidisciplinary intervention, whereas health professionals were involved in both kinds of intervention and provided care and treatment for all participants according to the hospital’s clinical standards. It would therefore be expedient to search for facilitation of RTW by the multidisciplinary intervention in subgroups needing assistance to perform their job, to make arrangements with their employer or other occupational issues.”
Also new is the paragraph on page 18:
“We also expected to see other subgroups, such as those with low social support from a supervisor or those with high work pace, benefit more from a multidisciplinary than from a brief intervention, but this was not the case. The backdrop against which the present study of a wide range of work-related factors was launched was the lack of previous studies on very specific work-related issues that should be considered by multidisciplinary teams. Some of these factors apparently affected the outcome of the multidisciplinary effort, whereas others were not important. This should be further examined in new studies.”

A major revision of the Analyses section was carried out to be more specific on the following topics:

- Claimants were not excluded from the new study
- Paragraphs on claimants have been revised and moved from the Introduction and Discussion sections, which should make it more clear why “claimants” in the Danish context is different from claimants in other systems and why the analytical step that excluded claimants was introduced
- Claim status was reported by the participants in the baseline questionnaire, that is, claim status was established before inclusion and randomisation.
- Besides the more elaborate description of the analyses, the issue of multi-co-linearity is also discussed in the Discussion section, page 20.
- “multivariate” was corrected
- the power issue has also been included in the Analyses section and in the Discussion page 20. We became convinced that we had a problem with the statistical power of the analyses in the new study, and recalculated the results in Table 4 without adjusting for other baseline factors than gender.

4.

We have included some of the requirements of STARD. In particular, the following paragraphs were added or revised:

- “Patients from nine municipalities in the Central Denmark Region were referred by their general practitioner (GP) based on the inclusion and exclusion criteria. The criteria were re-evaluated at The Spine Centre, Region Hospital Silkeborg, where the study was performed. All patients referred to the Spine Centre who adhered to the inclusion and exclusion criteria were included in the study.”

- “The methods used for clinical examination have been described previously [14]. Reassuring explanations for pain and advice on a gradual increase in physical activity were provided. Subsequent randomisation was performed by a secretary on the basis of block randomisation generated by an externally located computer. At the following consultations, both participants and caregivers were aware of the result of the randomisation. Data analyses were performed by researchers outside the hospital”

- “Cases with missing values in any of the baseline variables in each model were excluded from the analysis”.
Another important requirement is the description of the flow of participants. We have briefly described this in the Methods section, but a flow diagram is not included, as we refer to the main paper reporting from the results of the randomised trial, where such a diagram is shown. However, it will be possible to incorporate the same diagram here, if the editors find it appropriate.

The Figure legends have been changed to provide more information. RTW is defined as return to work and two sentences have been added: “Fraction of participants with RTW is shown during follow-up. The first visit at the clinic is at week 0.”

Apparently, it is unclear whether we have copy pasted the results from our RCT on our entire population, or we have already excluded claimants. We have revised the Analyses section to clarify this.

5.

Plausibility has been addressed as described above.

The paragraph on prognostic factors has been deleted and the discussion is now focused on factors that mediate or moderate the effects of the interventions.

A reference to Heymans et al. was included page 19: “Low-intensive back school has also been reported to have the same or a slightly better effect on return to work than high-intensive back school”. The reference was added to the reference list.

6.

Limitations are now more discussed on pages 20-21. Some of the central new paragraphs would be:

“A drawback of the attempt to identify as many factors as possible was the large number of analyses and the associated risk of reporting spurious results. Thus, 5% of all associations would be expected to be statistically significant by chance. This risk was acknowledged by the re-analysis and confirmation of results in a new sample of sick-listed employees, which indicated that the different effects in subgroups did not occur by chance. “

“Thus, the risk of reporting erroneous results due to mass significance, problems with multi-collinearity and bias in post-hoc analyses was reduced by conducting similar analyses with similar results in a new study. However, the next and final step would be to conduct a new randomised trial with specific hypotheses and advance stratification by relevant subgroups.”
Response to reviewer: Eva Skillgate

We greatly acknowledge the critical points and comments of the referees. The manuscript has now been changed in accordance. For more detailed answer, please see below. In the revised manuscript the paragraphs, which are new or considerably revised, are underlined. Underlining can easily be removed by “not accepting changes”.

The title has been changed:
“Subgroup analyses on return to work in sick-listed employees with low back pain in a randomised trial comparing brief and multidisciplinary intervention.”

Abstract

“Clinical” has been changed to “comparative”

"One year RTW” has been deleted and the sentence rephrased as follows: “Using data from a national database, we defined RTW as no sickness compensation benefit disbursement for four consecutive weeks within the first year after the intervention.”.

In the Methods section it is now clarified that sickness compensation benefit was due to LBP, however, other reasons for sick-listing later on could not be excluded: “At the first interview in the clinic, it was ensured that sick leave was primarily due to low back problems.”

More information has been added to the sentence on interaction term: “An interaction term consisting of a baseline variable*intervention group was added to the multivariable regression model to analyse whether the effects of the interventions were moderated by the baseline factor “

The Results section has been rewritten to report on subgroups of patients rather than “interaction effects”: “The multidisciplinary intervention group ensured a quicker RTW than the brief intervention group in a subgroup with low job satisfaction, notably when claimants were excluded. The opposite effect was seen in the subgroup with high job satisfaction. When claimants were excluded, the effect was also in favour of the multidisciplinary intervention in subgroups characterised by no influence on work planning and groups at risk of losing their job. Inversely, the effect was in favour of the brief intervention in the subgroups who were able to influence the planning of their work and who had no risk of losing their job due to current sick leave.”

Conclusions have also been rephrased: “Multidisciplinary intervention seemed more effective than brief intervention in subgroups of patients with low job satisfaction, no influence on work planning and feeling at risk of losing their jobs due to their sick leave as compared with subgroups not fulfilling these criteria.”

Introduction

The aim is now stated as in the abstract:
“The objective of the present explorative study was to study whether particular subgroups identified on the basis of work-related factors would benefit more from the multidisciplinary than from the brief intervention.”

The sentence “In our view…” has been deleted.

Methods

In the Methods section it is now clarified that sickness compensation benefit was due to LBP: “Reasons for sick leave or other health data are not available in the database, but such information was obtained at the first interview in the clinic. At this meeting, it was confirmed that sick leave was due primarily to low back problems.”

The section on Analyses has been considerably modified. Hopefully it is now more clear why the tests were performed (a reference is added at the beginning) as the procedure is explained in detail. It should be clearer that interaction terms were added to identify subgroups and the full models were adjusted for other factors (including possible confounders). It is explained how the assumption of proportional hazards was checked, but this has also revealed a problem with the previous analyses. Previously we only checked the individual factors, but now we have checked for proportionality in the full models and realised that the assumption was not fulfilled for one of the baseline factors, “support from colleagues”. This factor has now been deleted from tables 3 and 4 and the other results have been adjusted accordingly (as this factor no longer is adjusted for in the other models).

Results

It is now reported more directly which subgroups showed faster RTW in the multidisciplinary or brief intervention groups. The new paragraph is: “In the next step in which multivariable models were adjusted for age, gender and other baseline factors, the subgroup with high job satisfaction in the brief intervention group returned earlier to work than the corresponding subgroup in the multidisciplinary intervention; and the effect was the opposite in the subgroup with low job satisfaction, especially when claimants were excluded (Table 3). When claimants were excluded, the effect was also in favour of the multidisciplinary intervention in subgroups characterised by no influence on work planning and at risk of losing their job, whereas the effect was in favour of the brief intervention for the subgroups who had influence on work planning and no risk of losing job due to current sick leave (Table 3).”

Also, in the last part of the Discussion a paragraph has been added to ease the interpretation of the statistical analyses of subgroups: “However, the statistical power was low and the interaction effects were not statistically significant in the new study. Furthermore, the HRRs within specific subgroups were not consistently different from 1, even when the interaction was statistically significant. The test for interaction only revealed differences between the HRRs of two mutually exclusive subgroups. The subgroups composed of the combined subgroups of 1) no influence on work planning/risk of losing job and 2) influence on work planning/no risk of losing job was an example of this. Both in the original study and in the new study, the interaction of these subgroups on the intervention effect was statistically significant. However, in the original study, the HRR was significantly lower than 1 (brief intervention more
effective) in the subgroup with influence on work planning/no risk of losing job, whereas the HRR was not significantly higher than 1 in the other subgroup. In the new study, the HRR was significantly higher than 1 (multidisciplinary intervention more effective) in the subgroup with no influence on work planning/at risk of losing job, whereas the HRR was not significantly lower than 1 in the other subgroup.“

In Tables 3 and 4 a footnote has been added to explain the “no moderator” expression

Discussion

The issues on methodological limitations have been expanded considerably. The following paragraph has been added: 
“Another potential problem is that of multi-co-linearity between work-related factors. It is clear that it was often the same participants who assessed that they had low social support, low job control, low work ability and so forth. However, these factors do measure different aspect of working life and we were interested in identifying as many factors as possible with a modifying effect. The correlation between independent variables increased the risk of confounding, which was minimised by adjusting for other baseline factors in the multivariable regression models. The statistical power was relatively low for analyses of interaction. We therefore decided to adjust only for baseline factors within the same domain, i.e. the work-related or the health and work-related domain. This procedure should have eliminated the most likely candidates for confounding, but could not rule out that other factors confounded the results. A drawback of the attempt to identify as many factors as possible was the large number of analyses and the associated risk of reporting spurious results. Thus, 5% of all associations would be expected to be statistically significant by chance. This risk was acknowledged by the re-analysis and confirmation of results in a new sample of sick-listed employees, which indicated that the different effects in subgroups did not occur by chance.“

Also, at the end of the discussion it was rephrased that:
“Thus, the risk of reporting erroneous results due to mass significance, problems with multi-co-linearity and bias in post-hoc analyses was reduced by conducting similar analyses with similar results in a new study. However, the next and final step would be to conduct a new randomised trial with specific hypotheses and advance stratification by relevant subgroups”

The paragraph on potential underestimation of RTW has been deleted

The new information on claimants in the Discussion has been moved to the Methods section.

Conclusion

The conclusion has been rephrased. The new version is: “Multidisciplinary intervention seemed more effective than brief intervention in subgroups of patients with low job satisfaction, no influence on work planning and feeling at risk of losing their jobs due to their sick leave as compared with subgroups with high job satisfaction, influence on work planning and no perceived risk of losing their jobs. The findings were confirmed in a new subset of patients receiving similar interventions.”
The questions on figures in Table 3 and 1 is no longer relevant as these figures have been deleted. The characteristics of the participants in the new study have been added to Table 1. Also, in the Results section a paragraph on clinical findings has been added:
“Non-specific LBP was found in 191 (54%) patients. Radiculopathy was found in 112 participants (32%) and the remaining 48 participants (14%) were classified with other diagnoses (e.g. disc herniation without radiculopathy, spondylolisthesis). Later, 33 participants (9%) underwent surgery because of lack of improvement by conservative therapy (16 participants in the brief intervention group and 17 participants in the multidisciplinary intervention group). Mean pain levels on the LBP rating scale were 32.7 (SD=12.4) in the brief and 31.6 (SD=12.1) in the multidisciplinary intervention group.”

And later in Results from the new study:
“The mean pain level on the LBP rating scale was 35.2 (SD=11.7) in the brief and 35.1 (SD=12.1) in the multidisciplinary intervention group.”