Author's response to reviews

Title: A systematic review of the etiopathogenesis of Kienbock's disease and a critical appraisal of its recognition as an occupational disease related to hand-arm vibration

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Author's response to reviews: see over
Dear Mr. Shipley,

Thank you for your time and consideration. I also would like to thank the reviewer Simon Dagenais for the thorough peer review and his expertise. The authors have made the necessary modifications (marked in red) in response to the recommendations of the reviewer below and in the original manuscript. Since the systematic review has been updated until July 7th, 2012, we hope that timely publication in BMC Musculoskeletal Disorders will now be made possible.

Reviewer: Simon Dagenais
Reviewer’s report:
The revised manuscript is somewhat improved over the original. Authors have addressed many of the reviewers’ comments, but not quite to my satisfaction. For example, authors cannot simply dismiss discussing studies reporting an association between vibration and KD because meta-analysis was not possible; results still need to be discussed (e.g. x% of studies reported a positive/negative association, which varied from A to B). As highlighted below the manuscripts discusses details of every single cohort study: “Further, 16 studies were identified that argued against an etiopathologic role of hand-arm vibration (fig. 3). Four cohort studies for and four cohort studies against a causal relationship were screened to perform a meta-analysis on the strength of association of KD and hand-arm vibration. One cohort study was excluded from the review due to an investigation of other predominant disease risk factors (appendix). Three cohort studies lacked a control group (table 1). None of the cohort studies specified the total vibration exposure dose. All of the studies used only one or two X-rays as diagnostic criteria. The largest cohort study included 580 exposed versus 90 unexposed workers. None of the previously described quality criteria to decrease susceptibility to bias as described by Sanderson et al. (18) have been met in the identified retrospective cohort studies (appropriate definition of inclusion or exclusion criteria for cohorts and controls to control selection bias; appropriate measurement methods of vibration exposure and appropriate diagnosis of KD to control incorporation bias and imperfect-standard bias; appropriate methods outlined to deal with any design-specific issues such as recall bias, interviewer bias and biased loss to follow or blinding; appropriate design and analytical methods to control confounding bias; appropriate use of statistics for primary analysis of effect to control confounding; declarations of conflict of interest or identification of funding sources). Retrospective cohort studies revealed an average incidence of KD of 0.7% (10/1344) among chain-saw workers and no KD in any of the control groups (0/753) (Fisher’s Exact Test p=0.017) (table 1).

Table 1 discusses all relevant details of the cohort studies such as:
Authors still need to address study quality and how each it was evaluated rather than state that none of the studies met all criteria for quality.

Response to reviewer Eugene K Wai in letter to the editor from the July 11th, 2012.

b9 - What method was used to assess the quality of studies identified.

Modification:
"RESULTS: Systematic review: None of the previously described quality criteria to decrease susceptibility to bias as described by Sanderson et al. (16) have been met in the identified retrospective cohort studies (appropriate definition of inclusion or exclusion criteria for cohorts and controls to control selection bias; appropriate measurement methods of vibration exposure and appropriate diagnosis of KD to control incorporation bias and imperfect-standard bias; appropriate methods outlined to deal with any design-specific issues such as recall bias, interviewer bias and biased loss to follow or blinding; appropriate design and analytical methods to control confounding bias; appropriate use of statistics for primary analysis of effect to control confounding; declarations of conflict of interest or identification of funding sources)."

Although there are guidelines on the reporting of observational studies (17), there is no consensus on quality assessment of such studies (16). The authors are not aware of valid, reliable and meaningful quality criteria for the scoring of expert opinions, case reports and case series which account for more than 90% of the published literature.

Authors should understand that being underpowered is only an issue if no association is found. As this is not discussed further, it cannot replace a full discussion of association in the studies uncovered.
Response to reviewer Eugene K Wai in letter to the editor from the July 11th, 2012.

b10 - Studies with no significant results may have been underpowered. How was this accounted for? Besides the questionable quality of the studies, all studies were underpowered:

"Taking into account the fact that KD is a rare disease, we would expect its prevalence to be much lower than 1/1,000. Assuming a prevalence of 5% among vibration exposed workers, 516 cases and 516 controls would be necessary to verify an odds ratio of 2 in a case control study design (significance level: 5%; statistical power: 80%) (18). [...] No study came up with a large enough number of cases to account for the rarity of the disease."

The authors therefore conclude: "The herein identified cohort studies do not permit a meta-analysis of the association of hand-arm vibration and KD."

Overall, the methodology used in this review is not fully transparent, leaving open the possibility that authors did not have pre-specified conditions under which each of the Bradford Hill criteria could be met, and simply determined how this would be done after viewing the results to support their opinions.

1. See response to b9.
2. "We carried out a systematic review of the Ovid/Medline, Embase, and the Cochrane database for the keywords "Kienböck's disease" and "etiology" including different spellings and synonyms (appendix) following PRISMA guidelines (15)."
3. ". Two authors independently reviewed all included full-text articles to identify 1) the level of evidence presented; 2) predisposing factors, risk factors and etiopathological hypotheses of KD; and 3) the author's judgment if the discussed factors and hypotheses were maybe or unlikely linked to the etiology of KD. Disagreements were resolved through consensus or by consultation with a third reviewer. The level of evidence of every article was evaluated according to the criteria of the Oxford Centre for Evidence-Based Medicine (www.cebm.net). Non-systematic reviews of the scientific literature were classified as expert opinions. Predisposing, risk and causative factors were categorized according to the author's judgment if they were maybe or unlikely linked to the etiology of KD while factors interpreted as mere coincidences (e.g. confounding factors) and previously unreported in the literature as being causative were not documented. Studies which found no significant results regarding the association of any of the discussed factors, or articles arguing against an etiologic role of certain factors, were defined as null studies. Since technical terms have changed over the large period of time encompassed by the study and since no clear distinction has been made along the reviewed literature, repeated microtrauma, repetitive loading, repetitive strain, cumulative trauma and hand arm vibration were considered synonyms."

4. Response to reviewer Eugene K Wai in letter to the editor from the July 11th, 2012: b6 - what methods of bias reduction were employed to identify and exclude articles identified in the search. "Two review authors independently assessed the eligibility of retrieved papers and resolved disagreements by discussion. We documented reasons for exclusion (appendix)."

For a detailed list of exclusion criteria please refer to the appendix:

"Excluded (other issues: influence of arthrosis on ulnar variance, spontaneous course of KD, osteochondritis dissecans, complication of silicone implant for KD, carpal malalignments, osteonecrosis of scaphoid, KD classification); Excluded (Therapy/Diagnosis)"

Language bias was reduced by including all articles published in English, French or German. Selection bias was reduced by using different keywords "Kienböck's disease" and "etiology" including different spellings and synonyms. Inclusion bias was reduced by using several different electronic databases and by "searching other resources references of indexed articles, bibliographies from university libraries, and from an extensive internet literature search as well as presentations from the International Meeting for Kienböck's Disease in Vienna (14.-15.05.10)."

Authors need to present much more clearly how they would have determined that each of the Bradford Hill criteria could have been met, rather than stating they were not fulfilled.
Although it may seem beyond the scope of this manuscript to elaborate study designs that could bring about evidence for or against every single criteria from the ILO recommendation, the authors gave examples of how causality could be determined:

**Strength of association:** “Taking into account the fact that KD is a rare disease, we would expect its prevalence to be much lower than 1/1,000. Assuming a prevalence of 5% among vibration exposed workers, 516 cases and 516 controls would be necessary to verify an odds ratio of 2 e.g. in a case control study design (significance level: 5%; statistical power: 80%) (19). The number of required cases and controls would be even higher if confounding effects were also to be taken into account (20) while the calculation of the relative risk in cohort studies would require a population of several thousand.”

**Consistency:** Response to reviewer Eugene K Wai in letter to the editor from the July 11th, 2012: b14-
The authors argue that only 35% of identified studies discussed vibration as a possible etiology as a sign of inconsistency. However, A. it is likely that not all papers had the mandate to consider vibration. What is the percentage using this? and B. consistency would apply to observed empirical observations and not what authors chose to put in their paper.
"The finding that only 35% of published literature on the etiopathology of KD favours a causal relationship between KD and hand-arm vibration, underlines the lack of scientific consensus. On the other hand, null studies regarding the association of KD and hand-arm vibration represent 10% of published literature and 23% of all articles discussing an etiopathologic role of hand-arm vibration. Four out of 7 cohort studies on the influence of hand-arm vibration conclude that there is no association. Among the 4 controlled cohort studies 2 conclude that there is no association (Table 1)."

To our knowledge there is no rational to define and quantify all papers that "had the mandate to consider vibration" as a base line reference for consistency. Besides already acknowledged publication bias, it reasonable to assume that consistent observed empirical observations are consistently reported on in literature. (Consistency: Different research reports have generally similar results and conclusions (12).)

Authors also need to soften the tone of the manuscript to indicate that the issue of causality cannot be resolved with one article. The strident tone used loses credibility as it seems authors are trying to prove their opinion rather than objectively evaluate the truth as intended. See corrections in red.

We agree with the reviewer and several changes have been made throughout the manuscript to soften the tone especially in the discussion and conclusion. In addition, the following paragraphs were removed:

**Results; Consistency:** “The appearance of KD in the List of Occupational Diseases 100 years after Kienböck's investigations is surprising since reviews and expert opinions of occupational disease caused by hand-arm vibrations in 1987, 1998 and 2002 concluded that the allegation that KD may be typically induced by hand-arm vibration had not been documented with validity (21-23).”

**Discussion:** “The Occupational Disease Ordinance for the recognition of KD from the German Federal Ministry of Labour and Social Affairs lists KD as being predominantly diagnosed in underground workers and refers to a retrospective study from 1934. Herein the author reviewed 1,000 X-rays of underground workers with degenerative joint disease recognized as being occupational in origin and diagnosed 130 cases of KD (55). Yet simple X-ray cannot reliably differentiate the rare disorder of KD from other frequent cases of lunate fractures and pseudoarthrosis, intraosseous ganglia and scapholunate advanced collapse. In contrast, alterations in lunate bone relief are generally appreciable on X-rays with the exception of KD in stage 1. X-ray sensitivity is therefore likely to be greater than the specificity, leading to an overestimation of KD prevalence. Studies based on X-ray are necessarily subject to substantial incorporation bias since both sensitivity and specificity of even high resolution MRIs and CT-scans rarely reach 100% (56). Radiologic measures are often subject to technical and human errors (eg, are estimated visually), and radiologists may vary in their interpretation of diagnostic imaging. Imperfect standard bias occurs when the reference-standard
procedure yields results that are not nearly 100% (57). Yet methods of bias reduction in radiologic imaging were not applied in the reviewed studies.”

Conclusion: “The Occupational Disease Ordinance for the recognition of KD from the German Federal Ministry of Labour and Social Affairs lists KD as being predominantly diagnosed in underground workers and refers to a retrospective study from 1934. Herein the author reviewed 1,000 X-rays of underground workers with degenerative joint disease recognized as being occupational in origin and diagnosed 130 cases of KD (55). Yet simple X-ray cannot reliably differentiate the rare disorder of KD from other frequent cases of lunate fractures and pseudarthrosis, intraosseous ganglia and scapholunate advanced collapse. In contrast, alterations in lunate bone relief are generally appreciable on X-rays with the exception of KD in stage 1. X-ray sensitivity is therefore likely to be greater than the specificity, leading to an overestimation of KD prevalence. Studies based on X-ray are necessarily subject to substantial incorporation bias since both sensitivity and specificity of even high resolution MRIs and CT-scans rarely reach 100% (56). Radiologic measures are often subject to technical and human errors (eg, are estimated visually), and radiologists may vary in their interpretation of diagnostic imaging. Imperfect standard bias occurs when the reference-standard procedure yields results that are not nearly 100% (57). Yet methods of bias reduction in radiologic imaging were not applied in the reviewed studies.”

The manuscript should also be proofed more thoroughly. For example, the abstract still says literature search ended in January 2012 rather than July 2012.

Done.

Yours sincerely,

Adelana Santos Stahl

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