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

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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 reviewers David Ring, Eugene K Wai and Simon Dagenais for the thorough peer review and their expertise. The authors have made the necessary modifications (marked in red) in response to the recommendations of the reviewers 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: David Ring
My only comment would be to hypothesize in the Discussion section that the ideas here apply generally to most diseases.
Etiology is one of the most difficult things to establish and allowing something to be labelled work-related has very important negative consequences.

Modifications:
"DISCUSSION: The etiopathology is of paramount importance for the treatment, prevention and, if work-related, for the prognosis of KD as for many other diseases (1;2)."
"CONCLUSION: The negative impact of speculative causal associations (association between power lines and cancer (3), silicone breast implants and rheumatologic illness (4), mobile phones and brain tumors (5)), urges us to carefully reflect data using the appropriate methodological safeguards and statistical tools. The examination of the Bradford Hill criteria regarding the relationship of occupational risk factors and carpal tunnel syndrome (6), occupational physical activity and low back pain (7) has challenged our preconceptions by finding conflicting evidence to support causal relationship. Moreover it has been reported that Workers’ Compensation Board claim adversely impacts outcome among individuals with low back pain (8) and carpal tunnel syndrome (2)."

The best approach for the worker and society is to assume that a disease is not related to work until soundly proved otherwise. History is clear that the concept that work can harm your body has done far more harm than good and we need to protect people from these harmful ideas. This goes beyond work to things like power lines and cancer and silicone breast implants and systemic illness.

May I ask you for some advice? In your article on CTS from 2008 you write: "The qBHs rates consistency as follows: 4 points are assigned if more than 75% of the studies confirm an association; 2 points are assigned if between 75% and more than half of the publications confirm association; 1 point is assigned if half of the studies confirm an association; and no points are assigned if either there were fewer than 6 studies addressing causal association or the association was confirmed in fewer than half of the studies." Are these proportions in relation to all studies that investigated biological and occupational etiologies of CTS, in relation to studies that only investigated occupational risk factors or in relation to studies that only investigated a specific occupational risk
factor (i.e. vibration or stressful manual work)? Do the compared "for and against" studies need to meet uniform quality criteria (number of cases and controls, methods of bias control...)?

Reviewer: Eugene K Wai

MAJOR COMPULSARY REVISION:

A1. In causality assessment, the absence of association strongly argues against causality. However, I am not sure if the author adequately demonstrated if there was evidence for or against association, stating that there was too much heterogeneity to do a meta-analysis. However, there are qualitative systematic methods to assess for association in the literature when there is heterogeneity. "Qualitative methods, on the other hand, can often directly investigate these causal processes, although their conclusions are subject to validity threats of their own." (9)

Although they represent an interesting philosophical approach, it is questionable whether qualitative methods are reliable, valid and reproducible in the context of scientific research of the etiopathology of rare diseases.

I would like to see some results for association. If there is no association then further assessment of the other criteria is moot. If there is association, then there should be more research directed at assessing the other BH criteria.

Table 1 describes important quality criteria of the retrospective cohort studies, study characteristics (number of workers, number of KD cases among exposed, control group, exposition period), risks of bias (diagnostic criteria, anamnesis, clinical examination, confounding variables) and the results (incidence of KD in workers exposed and unexposed to hand-arm vibrations) according to PRISMA guidelines as well as the author's conclusion.

We therefore conclude: "The herein identified cohort studies do not permit a meta-analysis of the association of hand-arm vibration and KD since they encompass heterogeneous vibration exposures, use imprecise diagnostic criteria, do not include confounding effects or blinded radiologic evaluation. No study came up with a large enough number of cases to account for the rarity of the disease."

We believe that further assessment of the other criteria is important because:

1) We stated that a quantitative meta-analysis was not possible based on the studies of the association of hand-arm vibration and KD. That means, that we cannot say anything about a possible association and that the studies don't suggest an association but they also don't exclude any association. Therefore we find it useful to analyse all BH criteria whether or not an association could be found in the studies.

2) Association is not a sufficient parameter for causality even if it is statistically significant in multiple homogeneous well designed cohort studies (10).

3) Bradford Hill, unlike the International Labour Organization, did not conceive of the satisfaction of the "aspects of statistical association" as necessary conditions (singularly or jointly) for a specific statistical association being a causal relation (10).

4) Because the quality of studies is low (great susceptibility to bias) and because a type I error cannot be excluded, all Bradford Hill criteria were applied before deciding that the most likely interpretation of the observed effect is causation.

5) The Bradford Hill criteria "are tools, in the toolkits of people interested in making causal claims, for preliminary assessments of statistical associations. ...While satisfactions of causal criteria (such as the Bradford Hill criteria...) do not warrant causal claims, their judicious application is important and, perhaps in many cases, indispensable for identifying interesting statistical relationships that can then be subjected to a further, more analytically rigorous statistical examination (10)."

Other specific comments below:

DISCRETIONARY REVISIONS

ABSTRACT:

b1- evidence level 4 may not be understood by all readers and should be elaborated on

Modification:

"A total of 219 references was found. Of the included 152 articles, 140 (92%) reached the evidence level IV (case series)."
b2 - would have liked to see some results on association for all factors and evidence for the other BH criteria.

No other publication was found that evaluated other Bradford Hill criteria (i.e. experiment, biological gradient) as most publications have assessed association as being sufficient evidence for causality. Therefore no other Bradford Hill criteria could be systematically reviewed. The evaluation of all 57 identified factors possibly linked to the etiology of KD is beyond the scope of a manuscript entitled "a critical appraisal of its recognition as an occupational disease".

b3 - the final statement of the abstract suggests that there is strict criteria for evidence evaluation to be included in the ILO. The authors should either present these criteria in the intro or tone down the final sentence. Best I can tell, the authors have taken a statement from the ILO and applied their own criteria.

Modification:
"A causal relationship between hand-arm vibration and KD was evaluated according to the criteria of Bradford Hill (strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, biological coherence, experimental evidence and analogy), which are widely accepted in epidemiology for investigating and defining causality and have been adopted by the International Labour Organization (11;12)."

The reference above refers to the following quote from the International Labour Organisation:
"Two main elements are present in the definition of an occupational disease: 1) The causal relationship between exposure in a specific working environment or work activity and a specific disease; and the fact that the disease occurs among a group of exposed persons with a frequency above the average morbidity of the rest of the population. 2) The recognition of a disease as being occupational is a specific example of clinical decision-making or applied clinical epidemiology. Deciding on the cause of a disease is not an “exact science” but rather a question of judgement based on a critical review of all the available evidence, which should include a consideration of the following:
Strength of association: The greater the impact of an exposure on the occurrence or development of a disease, the stronger the likelihood of a causal relationship.
Consistency: Different research reports have generally similar results and conclusions.
Specificity: Exposure to a specific risk factor results in a clearly defined pattern of disease or diseases.
Temporality or time sequence: The exposure of interest preceded the disease by a period of time consistent with any proposed biological mechanism.
Biological gradient: The greater the level and duration of exposure, the greater the severity of diseases or their incidence.
Biological plausibility: From what is known of toxicology, chemistry, physical properties or other attributes of the studied risk or hazard, it makes biological sense to suggest that exposure leads to the disease.
Coherence: A general synthesis of all the evidence (e.g. human epidemiology and animal studies) leads to the conclusion that there is a cause–effect relationship in a broad sense and in terms of general common sense.
Interventional studies: Sometimes, a primary preventative trial may verify whether removing a specific hazard or reducing a specific risk from the working environment or work activity eliminates the development of a specific disease or reduces its incidence (12)."

INTRODUCTION:

b4 - Paragraph 3 - I would like a stronger argument that the ILO and ELOD requires proof of causality to be considered listing as an occupational disease. A. Association with a risk factor may be adequate for certain purposes and B. No evidence could imply that the evidence refutes a relationship or that there are no studies that have been done to date that adequately address the question.

The reference from the International Labour Organisation has been added to the manuscript.

Quote: "Deciding on the cause of a disease is (...) a question of judgement based on a critical review of all the available evidence, which should include a consideration of the following: strength of
association, consistency, specificity, temporality or time sequence, biological gradient, biological plausibility, coherence, interventional studies” (12).

b5 - Paragraph 4 starts off with a discussion of Bradford Hill's criteria and then finishes with a discussion on the history of association of KD with risk factors. I would have liked a more thorough discussion of B.H.'s criteria and specific issues of these as it relates on how the review is structured. Bradford Hill criteria are a wide spread tool for assessing evidence of causation since the original publication in 1965. Because the criteria have been adopted by ILO and because they have been applied to numerous speculative associations of occupational risks with CTS, with low back pain and many more ("In the last few years, causal relationships between vitamin D and cancer prevention [...], dietary factors and coronary heart disease [...], tea, flavonoid consumption and stroke [...], antipsychotic drugs and diabetes [...] as well as antidepressants in bipolar disorders [...] have all employed the Bradford Hill framework. (7)"), yet another discussion on the definition and limitations of the criteria would not have provided any new evidence. The limitations of the Bradford Hill criteria are acknowledged in the conclusion.

METHODS:
b6 - what methods of bias reduction were employed to identify and exclude articles identified in the search.
Modification:
"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)."

b7 - paragraph 3, what is an "occasional cause" of kienbocks.
Modification:
"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."

b8 - Strictly using the Oxford criteria may not be appropriate given the rarity of this disease. I doubt there would ever be any RCTs on this topic and as such and given the rarity of this disease likely never. As such the level of evidence will never get about level 4. There are other methods to assess level of evidence for rare diseases
Quotre from John C. Carey, Rare Disease Epidemiology, Chapter 5, The Importance of Case Reports in Advancing Scientific Knowledge of Rare Diseases, p. 79:
"The aims of case reports and case series are (13):
I. Astute observation of etiology and pathogenesis
II. Observations that add to the understanding of patients with a rare disorder
III. Observation providing lessons in differential diagnosis or in decisions regarding diagnostic testing (14)."
As quoted case reports and case series may serve for observation of etiology. However causality cannot be determined by case reports and case series. In the absence of large definitive clinical trials, systematic reviews and meta-analyses can help inform clinical guidelines and provide a stepping-off point for future clinical research (15). Although KD is a rare disease, proper designed cohort studies (level IIb) and meta-analysis of these (level Ila) are feasible and mandatory before claiming a causal
relationship between KD and hand-arm vibration in the absence of strong evidence supported by other criteria of Bradford Hill.

"There is an ethical case for objecting to a "small" study when a "usefully larger" one could be achieved." (14)

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.

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."

b11 - I would like to know that for the critical criteria of "unlikely linked to KD", that there was a stricter criteria than a reviewer concluding this after reading the paper. To reduce bias, were there any ad hoc criteria? Was there a structured assessment? It should be discussed how agreement was measured and presented in the results as evidence of validity of this approach

A systematic review of observational data must attempt to minimize or prevent sources of bias by developing explicit but also broad criteria focused on the evidence relevant to the question.

Two categories were set up:

1: author supporting or acknowledging the discussed hypotheses
2: author refuting the presented hypothesis

"METHODS: 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."

Modification:

"There was almost perfect agreement between two reviewers regarding the determination of 1) the level of evidence presented (98%; 3 disagreements in 153 articles); 2) the predisposing factors, risk factors and etiopathological hypotheses of KD discussed per article (95%; 7 disagreements in 153 articles); and 3) the author's judgment if the discussed factors and hypotheses were maybe or unlikely linked to the etiology of KD (99%; 2 disagreements in 153 articles). The high inter-rater agreement supports the reliability of the approach. On the other hand the attribution of explicit but also broad criteria (1: author supporting or acknowledging the discussed hypotheses, 2: author..."
refuting the presented hypothesis) might have led to an overestimation of consistency because of a tendency of authors to echo pre-existing hypotheses."

b12 - This paper purports to assess occupational risk factors but seems to limit to vibration. How about Trauma as an occupational risk factor?

"The purpose of this paper was to investigate the causal relationship between KD and hand-arm vibrations." The evaluation of trauma coinciding with KD is beyond the scope of a manuscript entitled "a critical appraisal of its recognition as an occupational disease".

Nevertheless, the authors have discussed the trauma hypothesis in the manuscript:

"Regarding the hypothesis of trauma, Wette notes “that uncomplicated reductions of lunate dislocation never display signs of osteonecrosis, not even in cases where the lunate had not been reduced (...) severe and direct wrist strain, leading to intra-articular distal radius fracture and to fractures of the perilunar carpal bones (...) never caused late secondary lesions of the lunate bone (...) Since we have never seen such cases of theoretically possible occurrences among our patients, we must as experts defend the point of view that the fracture theory is a hypothesis for which direct evidence is lacking” (19). Case reports of KD after perilunate and fracture dislocations are rare and their categorization is based on the observation of a hypersclerosis of the lunate in conventional X-rays (20) or a signal alteration, as it is characteristic for post-traumatic wrist MRI. Transient hypersclerosis of the lunate is well known in perilunate dislocations and should not be confused with KD (20-23). Even spontaneous palmar dislocation of the lunate in rheumatoid arthritis does not necessarily lead to osteonecrosis (24).

As other authors, we believe that in-depth analysis on causality with the approach of Bradford Hill needs to focus on one causal factor at a time (Lozano-Calderon S, Anthony S, Ring D. The quality and strength of evidence for etiology: example of carpal tunnel syndrome. J Hand Surg Am 2008 Apr;33(4):525-38. Kwon BK, Roffey DM, Bishop PB, Dagenais S, Wai EK. Systematic review: occupational physical activity and low back pain. Occup Med (Lond) 2011 Dec;61(8):541-8.)

RESULTS

b13- Association: The authors conclude that they could not do a meta-analysis to assess for association because of heterogeneity. However, qualitative assessments could be done to summarize if an association or trend exists or not.

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)."

The retrospective cohort studies on the incidence of KD in workers exposed and unexposed to hand-arm vibrations are analyzed in Tab. 1. Study characteristics (number of workers, number of KD cases among exposed, control group, exposure period), risk of bias (diagnostic criteria, anamnesis, clinical examination, confounding variables) and results of individual studies are detailed according to PRISMA guidelines.

b14- Consistency: 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.

Modification:

"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 in literature. (Consistency: Different research reports have generally similar results and conclusions (12).)

DISCUSSION
b15 - the authors should acknowledge that there summaries are limited likely by the poor quality of studies that are out there, which in part is limited by the rarity of this disease.

"Our study had several limitations, most of which are inherent to any systematic review and meta-analysis of literature." This statement implies that any systematic review and meta-analysis of literature is only as good as the quality of the papers reviewed.

Notwithstanding the severity of the disease; case series can not imply the existence of a causal relationship. High quality controlled cohort studies of the association of KD and hand-arm vibration are feasible. "The combination of rarity, severity and children makes research on rare diseases an emotive topic." (Chapter 3, Simon Day, page 42). Yet these conditions do not fully apply to KD. The poor quality of the reviewed studies is not due to the rarity of the disease but to the priorities of founding organizations.

Reviewer: Simon Dagenais

Summary
This manuscript reports on a systematic review examining evidence supporting a causal association between occupational exposure to hand-arm vibration and Kienbock’s disease.

General comments
This manuscript reports on an interesting and perhaps controversial topic that is likely of interest to clinicians, employers, patients, and policy makers, i.e. possible role of occupational exposure to KD. Classification of a condition as work-related can have a substantial impact on a variety of factors, including compensation, job modification, healthcare utilization, and prognosis. However, it can be very challenging to determine that a causal relationship is in fact present, particularly when there is a delay between exposure and clinical manifestation.

The authors have chosen to conduct a systematic review, which is an appropriate study design given the need to examine and synthesize all available scientific evidence. The authors have chosen to examine this evidence using a framework proposed by Sir Bradford Hill to determine the possible work-relatedness of health conditions. However, the methodology developed by the authors to interpret evidence using this framework is somewhat unclear, and it is difficult to determine if their conclusions are in fact supported by the evidence uncovered.

This systematic review of a total of 215 full-text articles uncovers the lack of evidence for a causal relationship between KD and hand-arm vibration:

"The herein identified cohort studies do not permit a meta-analysis of the association of hand-arm vibration and KD since they encompass heterogeneous vibration exposures, use imprecise diagnostic criteria, do not include confounding effects or blinded radiologic evaluation. [...] No valid association of hand-arm vibration and KD was found among the reviewed literature to sustain that hand-arm vibration represent a predisposing or risk factor for KD. Using the Bradford Hill evaluation of causality, the current investigation does not support hand-arm vibration as causative of KD."

As presented, the manuscript does not incorporate any of the actual findings in the text, relegating all results to the appendix. This makes it challenging for readers to understand why authors can dismiss some of the different aspects related to causation in only 1 sentence. It would be much more informative for authors to also describe summary findings within the text.

Findings are shown in figures Nr. 1 to 4 and Table 1. General results of the systematic review and of others discussed risk factors are discussed in 2 concise paragraphs while details of the review
concerning the 9 criteria for causation are presented in the same section. The appendix shows the list of publications and risk factors identified as well as the search strategy.

Authors also need to explain their methods in more detail, as it is unclear how they assessed and synthesized evidence to determine if certain aspects were met. Such methods should address, for example, the proportion of studies that would need to have similar findings in order to determine if consistency was present, etc.

To our knowledge there is no universally accepted cut off for consistency as there is for the arbitrary statistical significance testing (the p-value).

Another aspect that needs to be refined is related to study quality, distinguishing between reporting quality and methodological quality. If authors found 10 studies on a certain aspect, and only 5 of them were considered of high quality, would those be “neutralized” by 5 low quality studies? In other words, how does study quality get incorporated into synthesis of evidence?

This problem has been acknowledged and investigated:

"DISCUSSION: For studies regarding negative ulnar variance we found a significant higher level of evidence for “positive” studies (Wilcoxon test, p=0.038) (fig. 3)."

This manuscript reviews a total of 215 full-text articles of different evidence levels from the early 20th century until today. The authors reviewed the level of evidence, the number of cases of Kienböck’s disease and the study's conclusion regarding a causal relationship between KD and hand-arm vibration exposure of all 215 full-text articles (Fig 3). It is noteworthy that expert opinions, case reports and case series account for more than 90% of the published literature and that causality cannot be determined by expert opinions, case reports and case series. The authors also assessed specific criteria relevant to the question of all cohort studies (Tab. 1): "Professional sector; Country; Number of workers; Number of KD cases among exposed; Control group; Diagnostic criteria; Anamnesis; Clinical examination; Exposition period; Confounding variables; Author's conclusion regarding a causal relationship". Broader criteria as suggested by the reviewer Eugene K. Wai, were also assessed:

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)."

The interesting approach of David Ring with a quantitative Bradford Hill score does not seem to be a reasonable method for Kienböck’s disease because of "the poor quality of studies that are out there". Authors should also be aware that Bradford Hill did not propose a list of criteria that needed to be present in order to determine causality, as represented in this manuscript. Rather, he proposed a framework to evaluate different aspects, viewpoints, or characteristics to determine the possible relationship between exposure A and disease B in order to inform the clinical practice of occupational health and policy decisions. In his own words:

“What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause and effect hypothesis and none can be required as a sine qua non.”

The authors are aware of this continually re-quoted citation and referred to the limitation of the Bradford Hill criteria as follows:

"Independent of their significance, correlations do not suffice to determine causality. Despite certain limitations, several of Bradford Hill’s criteria when taken together do contribute to a more comprehensive causal theory (25)."
Rather than suggesting that individual criteria suffice to demonstrate causality the authors point out that the application of all criteria proposed by Bradford Hill and recognized by the International Labour Organization do not permit a causal association of KD and hand-arm vibration.

Authors should respect this original intention and approach the topic in a much more nuanced manner. The overall tone of the manuscript is much too rigid when dealing with a topic that requires balance, awareness of limitations, and acknowledgement of the difficulties surrounding determining causation. Other specific comments are made below.

The authors are very grateful for this comment as the most important conclusion of this systematic review is that the level of evidence and the poor quality of the studies urge a cautious interpretation of currently discussed hypotheses on the etiology of KD. The authors have made modification in this regard. Please note the comments of the reviewer David Ring.

Specific comments

Abstract
Search ends January 2012 – search is 5 months old already and will need to be updated before publication.

The search of all Databases has been updated:
New article added:

Specify levels of evidence presented

Modification:
"Level of evidence of the manuscript:
Systematic review of cohort studies with worrisome heterogeneity: IIb"

Avoid using term Bradford Hill "criteria", which gives a false impression of their use
Since the International Labour Organization also refers to "General criteria for identification and recognition of occupational diseases" (12), the authors would prefer not to use different terms to avoid confusion.

Quote of Andrew C Ward:
"Following the publication of the Surgeon General's Report, Austin Bradford Hill, in his 1965 Presidential Address to the Section of Occupational Medicine of the Royal Society of Medicine, asked under what circumstances we can justifiably pass from "an observed association to a verdict of causation" (26). In answer to this question, Bradford Hill recommended the use of the five criteria present in the Surgeon General's Report, and added four others, viz., biological gradient, plausibility, experiment and analogy (27). Although he described the circumstances whose presence permitted passing from an observed observation to a verdict of causation as "aspects of [a statistical] association" we should "consider before deciding that the most likely interpretation of it is causation" (28), the resulting nine criteria are now typically referred to as the "Bradford Hill Criteria" for causal inferences. It is true that writers such as Phillips and Goodman object to calling Bradford Hill's aspects of association "criteria", preferring instead the locution "causal considerations" (29), but they also concede that what Bradford Hill proposed is "frequently taught to students in epidemiology and referred to in the literature as 'causal criteria'" (30). Moreover, while commonly used in epidemiology and the health sciences since 1965 as a "central tool for the epidemiological community in grappling with the broader issues of causal reasoning" (31), the "basic outline of the modern set of criteria has," according to Kaufman and Poole, "evolved little" since their formulation by the Surgeon General's Advisory Committee and Bradford Hill (31). ...the use of causal criteria
complements many possible approaches that one may take to the task of justifying the claim that it is true (or false) that a statistical association is a causal relation (10)."

Define "evidence level IV"

Modification:
"A total of 219 references was found. Of the included 152 articles, 140 (92%) reached the evidence level IV (case series)."

How was the “quality” of the cohort studies assessed?

The specific quality criteria of the cohort studies are summarized in table 1:
"Table 1: Identification and summary of retrospective cohort studies on the incidence of KD in workers exposed and unexposed to hand-arm vibrations. 4 retrospective cohort studies (purple fill color) among chain-saw workers were included in a meta-analysis with 1344 exposed and 753 unexposed workers."

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)."

How did authors determine that the “discussed hypotheses are not fulfilled”?

Modification:
"ABSTRACT: Results: ...Evidence for the lack of consistency, plausibility and coherence of the 4 most frequently discussed etiopathologies was found."

The above mentioned résumé is explained in details in the following section:

"RESULTS: Bradford Hill Evaluation of Causality: 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 (32-34). The likeliness of an etiopathologic role of hand-arm vibration is less frequently discussed in literature, compared to negative ulnar variance, primary arterial ischemia or trauma (Fig 2). 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).

Biological plausibility:
Contrary to expert or to historical opinion, that “the lunate bone is the hand’s only cushion against impacts on the wrist” (35), biomechanical studies show that in a neutral position of the wrist 1/3 of the pressure is transmitted from the lunate onto the triangular fibrocartilage complex and 2/3 of the pressure onto the lunate fossa. In the working position of the wrist in ulna deviation, the lunate is however only in contact with the lunate fossa (36), and pressure is uniformly transmitted through the radiocarpal joint. Knowledge of the force transmission in the wrist would suggest osteonecrosis of the scaphoid in case of exposure to hand-arm vibration, since force transmission predominantly occurs through the scaphoid (37). There has been no plausible explanation on why the lunate may be the only bone subject to necrosis of the 30 bones of the upper extremity in hand-arm vibration. Exposure to low frequency vibrations has been claimed to induce inflammatory mediators that “lead to the liberation of cytolytic enzymes, disturbing the balance between cartilage removing and
cartilage forming processes and thereby accelerating the degeneration of cartilage” (38). To our
knowledge no evidence has so far been found to support this hypothesis.
The German occupational disease ordinance further refers to an anatomical study from 1944 in
which a mercury solution was injected into the brachial artery in neutral position with the wrist
extended, observing that the lunate remained void of mercury in the extension of the wrist (39). The
author’s conclusion that the working position of the wrist in jack-hammer work predisposes KD is not
plausible since KD would be a wide-spread disease if, as suggested, an extension of the wrist would
predispose to KD.
According to official epidemiologic data 1.2 million Germans are exposed to a daily vibration level
greater than A(8)=2,5m/s² (exposure action value in a 8 hours/day exposure), which does present a
potential health risk (40). On the basis of 4 new cases of KD recognized as an occupational disease in
2006 in Germany, the incidence can be estimated at 3:1,000,000 in exposed workers (41). In the
same year 418 new cases of KD were treated on an in-patient basis within the country’s overall
population of 80 million (42). Since every patient with KD does not necessarily receive in-patient
treatment, the incidence must exceed 5:1,000,000. These approximate figures infer that the
incidence of KD is higher in populations without exposure to hand-arm vibrations rather than with
exposure. Several explanations are possible: (I) patients with KD were treated twice per year on an
in-patient basis, (II) under-reporting, (III) a healthy worker effect (43), (IV) hand-arm vibrations are
not a risk factor for KD.
The vast majority of authors describe a rich and constant palmar and dorsal vascularization of the
lunate bone (44) which even in cases of complete de-vascularization does not undergo necrosis (45).
Therefore, malperfusion seems to be rather the consequence than the cause of KD. Of the many
known risk factors for infarction (Raynaud’s phenomenon, antiphospholipid syndrome, sickle cell
anemia, decompression sickness, smoking, hypertension, atherosclerosis) none has been shown to
be significantly associated with KD. Moreover, there is no evidence that anticoagulants used in
thrombotic disorders may be of value for KD. Since all necrotic tissue is avascular, the term avascular
necrosis is a pleonasm and should not be used further.
Regarding the hypothesis of trauma, Wette notes “that uncomplicated reductions of lunate
dislocation never display signs of osteonecrosis, not even in cases where the lunate had not been
reduced (...) severe and direct wrist strain, leading to intra-articular distal radius fracture and to
fractures of the perilunar carpal bones (...) never caused late secondary lesions of the lunate bone
(...) Since we have never seen such cases of theoretically possible occurrences among our patients,
we must as experts defend the point of view that the fracture theory is a hypothesis for which direct
evidence is lacking” (19). Case reports of KD after perilunate and fracture dislocations are rare and
their categorization is based on the observation of a hypersclerosis of the lunate in conventional X
rays (20) or a signal alteration, as it is characteristic for post-traumatic wrist MRI. Transient
hypersclerosis of the lunate is well known in perilunate dislocations and should not be confused with
KD (20-23). Even spontaneous palmar dislocation of the lunate in rheumatoid arthritis does not
necessarily lead to osteonecrosis (24).
Biological coherence:
The ability of bone to respond to mechanical stimuli has been known for over a century. Moreover
we now know that (I) bone preferentially responds to dynamic rather than static stimuli, (II) only
short durations of loading are necessary to initiate an adaptive response, and (III) bone cells
accommodate to customary mechanical loading environments (46). Daily exposure to high-frequency
whole body vibration over 1 year has shown to increase femoral trabecular bone density by 32% in
adult ewes with closer spacing of bone trabeculae, which is consistent with stronger bone (47).
Progressive mechanical loading results in adaptive bone strengthening (48), where as an abrupt
increase in the duration or intensity of mechanical loading may result in fatigue fracture (49). To our
knowledge no experimental evidence exists to date to conclude that a defined vibration magnitude,
frequency, direction or exposure time may induce osteonecrosis.”
What are the “criteria of the International Labour Organization”?
The reference from the International Labour Organisation has been added to the manuscript ("Identification and recognition of occupational diseases: Criteria for incorporating diseases in the ILO list of occupational diseases; Meeting of Experts on the Revision of the List of Occupational Diseases (Recommendation No. 194); (Geneva, 27–30 October 2009)").

Modification:

"A causal relationship between hand-arm vibration and KD was evaluated according to the criteria of Bradford Hill (strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, biological coherence, experimental evidence and analogy), which are widely accepted in epidemiology for investigating and defining causality and have been adopted by the International Labour Organization (12;50).

Quote from the International Labour Organization:

"Two main elements are present in the definition of an occupational disease:

1) The causal relationship between exposure in a specific working environment or work activity and a specific disease; and the fact that the disease occurs among a group of exposed persons with a frequency above the average morbidity of the rest of the population.
2) The recognition of a disease as being occupational is a specific example of clinical decision-making or applied clinical epidemiology. Deciding on the cause of a disease is not an “exact science” but rather a question of judgement based on a critical review of all the available evidence, which should include a consideration of the following:

Strength of association: The greater the impact of an exposure on the occurrence or development of a disease, the stronger the likelihood of a causal relationship.
Consistency: Different research reports have generally similar results and conclusions.
Specificity: Exposure to a specific risk factor results in a clearly defined pattern of disease or diseases.
Temporality or time sequence: The exposure of interest preceded the disease by a period of time consistent with any proposed biological mechanism.
Biological gradient: The greater the level and duration of exposure, the greater the severity of diseases or their incidence.
Biological plausibility: From what is known of toxicology, chemistry, physical properties or other attributes of the studied risk or hazard, it makes biological sense to suggest that exposure leads to the disease.
Coherence: A general synthesis of all the evidence (e.g. human epidemiology and animal studies) leads to the conclusion that there is a cause–effect relationship in a broad sense and in terms of general common sense.
Interventional studies: Sometimes, a primary preventative trial may verify whether removing a specific hazard or reducing a specific risk from the working environment or work activity eliminates the development of a specific disease or reduces its incidence (12)."

Introduction
Page 4, Paragraph 1
(KD) should be in parentheses after “Kleinbock’s disease”
Done
Remove subsequent written out words “Kleinbock’s disease” and use abbreviation
Done
How does the true etiology remain poorly understood?
The adjectives obscure the fact that the etiology is unknown.
"The numerous synonyms for KD (lunate malacia, aseptic, idiopathic, avascular or traumatic lunate necrosis) infer that the true etiology remains poorly understood."
Last sentence needs reference
Done
Page 4, Paragraph 2
First sentence needs reference
In last sentence – explain units of exposure dose
Modification:
"The necessary total vibration exposure dose was estimated on the basis of the mean exposure time relayed in 59 expert reports of suspected occupational disease (240 working days per year; daily exposition of 5h/d; minimal duration of exposition of 2 years; total vibration exposure dose 5.122 metres per square second) (51)."
evidence was found to support any of the nine Bradford Hill criteria. Therefore a causal relationship is very unlikely. It is more a medico legal debate how many criteria or conditions need to be fulfilled or how likely a causal relationship must be in order to be recognized as such.

Source of funding – what was the source? Did authors do this work for free?
"Disclosure of potential conflict of interest:
The authors declare that they have no conflict of interest. No funding or grants from any commercial source have been received in support of the research or preparation of the work for this study."
There was no source of funding for this work.

Methods
Page 5, Paragraph 1 (first full paragraph)
Which Cochrane database was used?
http://www.thecochranelibrary.com/view/0/index.html
Page 5, Paragraph 2
If only full text articles were included, what was excluded?
As stated in Fig. 1 and in the 2nd paragraph of the METHODS section, 5 articles were excluded.
"All articles not published in English, French or German were excluded (n=2). The full text of three articles was not available."

How was screening performed?
Please be more specific as the full electronic search strategy for the databases, including any limits used are described as specified in the PRISMA statements (56).
"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 (57)."

From the appendix:

Page 5, Paragraph 3
States 215 articles – figure 1 says 214
Has been corrected.

Third point – author’s judgment if discussed factors were linked – how was that determined?
A systematic review of observational data must attempt to minimize or prevent sources of bias by developing explicit but also broad criteria focused on the evidence relevant to the question.
Two categories were set up:
1: author supporting or acknowledging the discussed hypotheses
2: author refuting the presented hypothesis

"METHODS: 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."

Remove comma after “Studies” in 2nd last sentence
Done.
Add comma after “factors” in same sentence
Done.
Page 5, Paragraph 4
Again, “criteria” – framework?
See comments above.

What about controversies in using Bradford Hill? Is it “widely accepted”
"A causal relationship between hand-arm vibration and KD was evaluated according to the criteria of Bradford Hill (strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, biological coherence, experimental evidence and analogy), which are widely accepted in epidemiology for investigating and defining causality and have been adopted by the International Labour Organization (12;58)."

**Results**

*Page 5/6, Paragraph 5*

Is there a difference here between case series and cohorts?

A cohort study is defined as a study on a group of people who share a common risk exposure. Case series are defined as a report of more than 3 consecutive cases of Kienböck's disease.

“At least one of these 57 hypotheses...”. This sentence is unclear.

**Modification:**

"Of the 153 full text articles included in the systematic review, 59 articles (39%) refuted at least one of these 57 hypotheses."

“Irrelevant” is a strong word – rephrase.

**Modification:**

"Among the 15 most frequently discussed hypotheses that were referred to in at least 10 articles, at least 20% of published literature refuted a causal relationship for the following factors: trauma (bony or ligamentous); hand-arm vibration (repeated microtrauma, repetitive trauma, repetitive strain); embolism (infarction); genetic predisposition."

*Page 6, Paragraph 1*

Add comma after “Further”

**Done.**

Fisher’s Exact Test – what was comparator?

**Modification:**

"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)."

**Strength of Association**

*Paragraph 1*

“large enough number” – what is that number?

A reference point is given 2 sentences below:

"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%) (59)."

*Paragraph 2*

Why is odds ratio of 2 important?

The odds ratio is given as an example in order to give a reference point.

**Consistency:**

Use “KD” instead of writing it out

**Done.**

Remove word “any” before “validity”

**Done.**

“... only 35% of published...” – number is irrelevant

**Modification:**

"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)."
The given numbers allow an evaluation of consistency as defined by Bradford Hill: "Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect".

Last sentence “10%” – so a higher percentage supports an association?
Out of a total of 153 included articles 53 articles (35%) support causality and 16 articles (10%) refute causality. Out of 69 articles discussing causality of hand arm vibration 16 articles (23%) refute causality. To our knowledge there is no universally accepted cut-off for consistency (percentage of research reports about a specific causative factors that have similar results and conclusions (12)) as there is for the arbitrary statistical significance level (p-value<0.05).

Specificity
Paragraph 2
Does hand-arm vibration cause other diseases?
Vibration-induced white fingers (Raynaud’s phenomenon of occupational origin) has been associated with hand-arm vibration exposure. Recently the validity of Raynaud's phenomenon symptoms has been questioned (Youakim S. The validity of Raynaud's phenomenon symptoms in HAVS cases. Occup Med (Lond). 2008 Sep;58(6):431-5. Epub 2008 Jun 20). The authors are not aware of other evidence of a causal relationship other than strength of association (ie. consistency, specificity, temporality or time sequence, biological gradient, biological plausibility, coherence, interventional studies).

Quote from European Commission:
"There is moderate evidence that contracture of the palmar aponeurosis (Dupuytren's disease) may occur as an effect of HAV. The prevalence of musculo-skeletal diseases of the upper limb, shoulder or neck is increased in HAV-exposed but it has not been possible to separate the effect of HAV from the effect of other physical factors, i.e. force, repetition and posture. It is not clear if HAV induces bone injuries such as vacuoles and cysts. " (60)

Temporality
“Negative UV is the only hypothesis that meets the criterion of temporality” – why? Explain.
Why negative UV is the only hypothesis that meets the criterion of temporality is explained in the following sentence: "... since negative UV is a stable condition after epiphyseal closure", negative UV is present before KD in the adult. On the other hand: "... none of these experimental or clinical studies investigated whether the necrosis preceded the ischemia, trauma or hand-arm vibration exposure or vice versa."

Last sentence – what does this mean?
Modification:
"Methodical problems in research of rare diseases should not lead to negligence. Although proper designed prospective controlled cohort studies for rare disease demand a multi-institutional collaborative efforts and substantial funding, expert opinions, case reports and case series should not be accepted as sufficient evidence for causality."

Quote from Manuel Posada de la Paz, Rare Disease Epidemiology, Chapter 2, Rare diseases Epidemiology Research, p. 29:
"Like research into high-frequency diseases, rare disease research also uses epidemiological observational studies, and the quality of methods to be applied to rare diseases should be equal to high prevalence diseases in any way. (14)"

Quote from Simon Day, Rare Disease Epidemiology, Chapter 3, Evidence-Based Medicine and Rare Diseases, p. 49:
"Bradford Hill's nine viewpoints should also not be used as excuses to "make do" with lesser levels of evidence when better evidence is necessary. Difficulty and necessity are separate. Difficulty may be a reasonable excuse but is never an adequate substitute for higher levels of evidence when they are needed. [...] There is an ethical case for objecting to a "small" study when a "usefully larger" one could be achieved."

Biological gradient
Did any studies discuss dose-response?
No study was encountered that tested a dose-response relationship.
"Since a significant association of KD and hand-arm vibration is a prerequisite to determine a biological gradient, a biological gradient regarding the effect the vibration magnitude, frequency, direction, type of tools, duration and pattern of exposure or any other extrinsic or intrinsic conditions has not been validly documented for KD."

Experimental evidence
After 2007 fix punctuation
Done.

Last sentence – not if all other factors change (awareness, diagnostic criteria)
Modification:
"Nevertheless an increase in the recognition of KD as an occupational disease can be seen between 2002 and 2006 (61), despite the legal enforcement of preventive measures (62), although according to Hill the elimination of the exposure or agent should decrease disease incidence and while no evidence has been found to suggest that awareness or diagnostic criteria of KD have contributed to the increase."

Analogy
What about other conditions related to exposure to vibration?
Has been commented earlier:
"Biological coherence:
...To our knowledge no experimental evidence exists to date to conclude that a defined vibration magnitude, frequency, direction or exposure time may induce osteonecrosis."

Discussion
Page 9, paragraph 1
“selection bias” – how is that related to sensitivity/specificity and resolution
Modification:
"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% (63). 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% (64). Yet methods of bias reduction in radiologic imaging were not applied in the reviewed studies."

Page 9, Paragraph 1
Add “s” to represent in second last sentence
Done.

Page 9, Paragraph 4
How were 98% and 95% determined?
Modification:
"There was almost perfect agreement between two reviewers regarding the determination of 1) the level of evidence presented (98%; 3 disagreements in 153 articles); 2) the predisposing factors, risk factors and etiopathological hypotheses of KD discussed per article (95%; 7 disagreements in 153 articles); and 3) the author’s judgment if the discussed factors and hypotheses were maybe or unlikely linked to the etiology of KD (99%; 2 disagreements in 153 articles). The high inter-rater agreement supports the reliability of the approach. On the other hand the attribution of explicit but also broad criteria (1: author supporting or acknowledging the discussed hypotheses, 2: author refuting the presented hypothesis) might have led to an overestimation of consistency because of a tendency of authors to echo pre-existing hypotheses."

Page 9, Paragraph 5
Last sentence needs reference
Modification:
"Used in combination, these methods help to ensure that all relevant literature is accounted for, therefore minimizing retrieval bias (65)."

Conclusion
Explain “in dubio pro reo”
Modification:
"Yet the principle of "benefit of the doubt" does not apply to scientific expert reports or to the European Listing of Occupational Diseases (66)."

In dubio pro reo = Benefit of the doubt: refers to an adoption of a positive opinion or judgement when there is some but not sufficient evidence to think otherwise.

Last sentence – “clinical study” – does author mean to say multiple studies?

Modification:
"The task of medical expert reports to furnish proof of a causal relationship that has never been ascertained seems illogical as long as multiple studies have not been performed to provide valid evidence for a correlation of KD and the discussed hypotheses."

Yours sincerely,

Adelana Santos Stahl

Reference List


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