The need for scientific evidence in occupational disease assessment

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Why dealing with this topic?

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Essay

Why Most Published Research Findings Are False

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Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions,

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability

Why dealing with this topic?

- The diagnosis of an occupational disease presents to the physician two challenges:

1. the first is making an accurate diagnosis of a disease (a challenge which is typical of the medical profession);
2. the second is making an etiologic diagnosis, that is, assess causation (something which is not ordinarily required for most of medical specialties).

- Assess causation is very different from having an opinion about the origin of a disease, because of the consequences, in most social systems, of an established diagnosis of an occupational disease.

Why dealing with this topic?

In addition, in some jurisdictional systems, an established occupational disease may be subject to mandatory reporting and may even be a criminal offence.

Disease vs Disorder

- The focus of this presentation is an occupational “disease”: for this purpose, we need to distinguish between the two conditions (and later we will not deal with “disorders”).
- In the Occupational Medicine literature (especially the papers concerning musculoskeletal conditions) it is common to see the use of “disorder” interchangeably with “disease”, even if the two terms point to different conditions.
- In fact, "disease" denotes a condition characterized by the presence of specific signs and symptoms, functional impairment, AND structural changes.

Distinction between disease and disorder

(AMA Style Insider. Condition, Disease, Disorder. https://amastyleinsider.com/2011/11/21/condition-disease-disorder/)

Disease	Disorder
Disease denotes a condition characterized by functional impairment, structural change, and the presence of specific signs and symptoms. As an aside, Dorland's equates the terms illness and sickness with disease; while these are often used to indicate the state or experience of disease, they are also sometimes used as value-neutral alternatives for disease.	Disorder, in contrast, denotes a condition characterized by functional impairment without structural change and, while certain disorders or categories of disorders might be accompanied by specific signs and symptoms, their presence is not required for a condition to be termed a disorder.

Disease vs Disorder

- This is particularly important in the definition of musculoskeletal disorders, as the presence of pain in a body region does not necessarily indicate the presence of an underlying pathology, given the evidence of pain without structural changes or, at the contrary, the evidence of structural changes without pain.
- In conclusion, whereas a “disorder” is a condition which is associated to a certain degree of functional impairment, it has not the rank of a “disease”, lacking required the presence of pathologically relevant “structural changes”.

Disease vs “Adverse effect”

- An additional problem is the notion of “adverse effect”, a term generally used in toxicology and defined as: “a change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences” (Keller DA, Juberg DR, Catlin N, Farland WH, Hess FG, Wolf DC, Doerrer NG. Identification and characterization of adverse effects in 21st century toxicology. Toxicol Sci. 2012 Apr;126(2):291-7).
- Whereas an “adverse effect” is obviously undesirable (and the same is for a disorder) its detection, by current medical standards, does not amount to a diagnosis of a disease.
- Disorders, as well as adverse effects, must be considered in preventive activities (where the purpose is not limited, of course, to avoiding disease).

Occupational vs work-related

- In the Occupational Medicine literature (especially the American one) it is common to see the use of “work-related” interchangeably with “occupational”, even if the two terms point to different conditions, at least according to the original definition of the term "work-related".
- The term "work-related" was defined by a WHO working group (https://apps.who.int/iris/bitstream/handle/10665/40176/WHO_TRS_714.pdf?sequence=1&isAllowed=y Identification and control of work-related diseases: report of a WHO expert committee. WHO Technical Report Series 714, 1985)
- According to the original definition of the WHO working group “… in occupational diseases, there is a direct cause-and-effect relationship between hazard and disease".

Occupational vs work-related

"In work-related diseases, in contrast, the work environment and the performance of work contribute significantly, but as one of a number of factors, to the causation of a multifactorial disease. Occupational diseases therefore stand at one end of the spectrum of work-relatedness, where the relationship to specific causative factors at work has been fully established and the factors concerned can be identified, measured, and eventually controlled. At the other end, diseases may have a weak, inconsistent, unclear relationship to working conditions; in the middle of the spectrum there is a possible causal relationship but the strength and magnitude of it may vary."

Occupational vs work-related

In this presentation, “occupational” is to be intended as “caused by work”. This includes the case of a disease for which:

the work activity is an exclusive cause, or

the work activity is a necessary contributory cause, together with other factors (i.e., the disease would not have occurred, at that time, if the person had not performed that work activity), or

the work activity has influenced the course of the disease, which would have been more favorable if the person had not performed that work activity (a case which is usually referred to as a “work-exacerbated disease”, as, for example, in the case of asthma).

The need for an evidence-based approach

The need for an evidence-based approach

- Occupational physicians and other clinicians often are asked for an opinion as to whether or not a problem is work related. It is incumbent upon the clinician to make certain that any opinion given reflects careful analysis of all available clinical findings and high-grade scientific evidence (American College of Occupational and Environmental Medicine. Occupational Medicine Practice Guidelines. 2008).
- Although many countries and some international organizations (e.g., ILO) have developed their own lists of occupational diseases (the so called “scheduled diseases”), the minimum medical diagnostic and workplace exposure criteria needed for diagnosis and attribution are, generally, utmost generic as evidenced by the striking differences in national occupational diseases statistics (e.g., mortality for silicosis in US vs Europe).

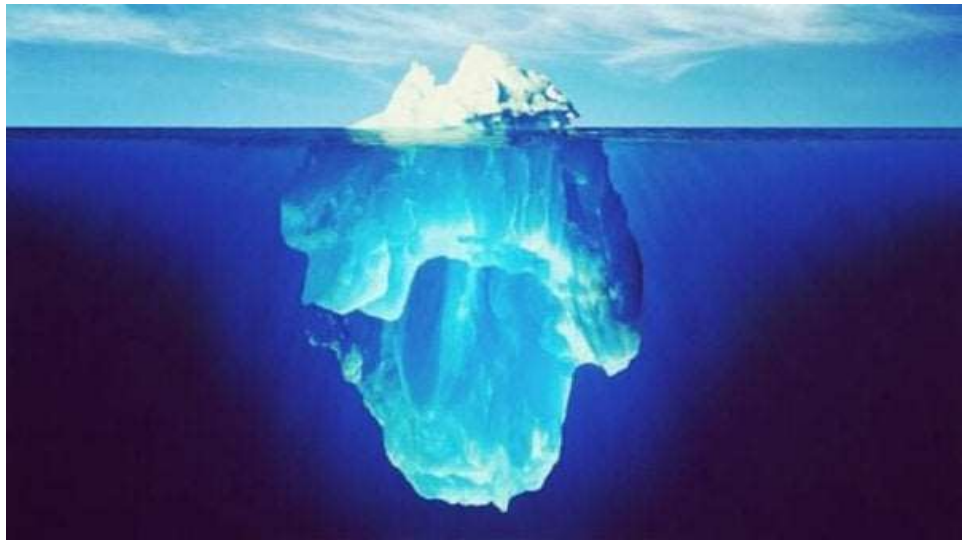
The need for an evidence-based approach

- Evidence-based criteria for diagnosis and attribution of occupational diseases will improve the assessment of the real “burden of disease” linked to specific risk factors, which is necessary for planning preventive interventions.

- The adoption of evidence-based criteria will also address the twin problems of under- and over-reporting of occupational diseases.

The need for an evidence-based approach

- **Under- and over-reporting** can be strongly influenced by non-medical factors, such as financial incentive to the worker, payments to health care providers, to attorneys or consultants, costs to the companies and so on.
- While **under-reporting** of occupational diseases is frequently emphasized, **over-reporting** has not received the same attention.



Too much medicine?

Too much medicine?

"Distinguishing the sick from the healthy has always been a fundamental challenge for medicine. A chief concern has been to guard against missing disease, with the focus on problems of underdiagnosis and undertreatment. Yet with the modern technological expansion of healthcare in rich developed nations, skeptical voices have long warned of the flipside-too much medicine. Mounting evidence about the threat to human health from overdiagnosis, and the harms and waste from unnecessary tests and treatments, now demand that we meet one of this century's key challenges: how to wind back medical excess, safely and fairly." (Moynihan R , Smith R . Too much medicine? BMJ 2002;324:859–60)

Overdiagnosis (and over-attribution)

"Overdiagnosis is one of the most harmful and costly problems in modern healthcare. It often triggers a cascade of overtreatment, although the two are not synonymous. To prevent and minimise overdiagnosis, we need more studies on the natural history of diseases, watchful waiting trials of very early/small or ambiguous abnormalities, studies of the effects of diagnostic language, intervention studies on known drivers of overdiagnosis, and studies of how to involve patients in decisions about diagnostic strategies. And we need to ensure that new disease definitions are based on evidence, not financial interests."
(Brodersen J, Schwartz LM, Heneghan C, et al. Overdiagnosis: what it is and what it isn't. BMJ Evidence-Based Medicine 2018;23:1-3.)

Rational approach to occupational diseases

- Occupational diseases are fundamentally defined by their etiologic characteristics: therefore, linking a disease to an occupational exposure requires several logical steps.

Rational approach to occupational diseases

The first step is **making an appropriate diagnosis of the clinical condition.**

The second step is assessing the extent of the **workplace exposure**.

The third step is determining **if workplace exposure is likely to have caused or exacerbated the condition**.

This latter step involves as a prerequisite a **thorough assessment of the existing medical literature on the association between the specific exposure and the disease**.

Rational approach to occupational diseases

- The diagnosis of a potentially occupational disease follows the typical procedures of clinical medicine with history taking, a focused physical examination, and relevant laboratory and/or imaging and/or pathology studies.
- Beyond this first step of making a clinical diagnosis, additional steps are necessary to identify whether there is a causal link to a workplace exposure, based on the analysis of workplace risk factors.
- Only very few diseases rarely occur without an occupational or environmental exposure (for example, most males with mesothelioma have had asbestos exposure).

Rational approach to occupational diseases

- Additionally, most diseases caused or exacerbated by work are clinically identical to the same diseases that do not have an occupational cause.
- Documentation of a substantial exposure increase the likelihood that a given disease in a given person is due to work activity.
- For causal attribution of a disease to a working activity, it is necessary to estimate exposures in the workplace through a review of all available data, to confirm the qualitative, quantitative and temporal parameters of the risk factors and their associations to the clinical history.
- History taking is not enough to establish a relevant occupational exposure (but it may rise the suspect of it).

Rational approach to occupational diseases

- Like the confirmation of diagnosis, the causal contribution from the exposure can also be considered on a probabilistic scale.
- For a disease to be considered occupational, it should be determined whether the workplace exposure is adequate in intensity and overall duration to induce the disease.

Rational approach to occupational diseases

- For a disease to be considered occupational, it should be determined whether the workplace exposure is adequate in intensity and overall duration to induce the disease.
- This may translate into the following questions:
  - From the collection of available data, are potentially causal exposures identifiable?
  - Is there an exposure factor (or a set thereof) in the work activity to which the worker has been exposed for the minimum exposure time and at the minimum intensity needed to induce the disease?
  - Is the latency of the disease appropriate based on the clinical history?
  - Has the role of non-occupational risk factors been adequately considered?

Rational approach to occupational diseases

- The recognition of an occupational disease should be based on 3 conditions:
  - the diagnosis, confirmed according to the best applicable criteria for a specific “disease”;
  - the assessment of workplace exposure to a given risk factor, performed in accordance with the best applicable criteria, specifying quantitatively frequency (how many times takes place), duration (how much time, altogether, in the working life) and intensity;
  - the determination, based on the literature, that the exposure is sufficient to cause the disease.

Rational approach to occupational diseases

- The 3 conditions will be illustrated through examples applied to musculoskeletal diseases, the most frequently reported "occupational" diseases in Italy :
  - criteria for the quality of the diagnosis of a disease (diagnostic criteria);
  - criteria for the quality of the assessment of an exposure to occupational risk factors;
  - criteria for the overall likelihood that a worker has an occupational disease (including criteria for the likelihood that non-occupational factors are the cause of the disease).

Diagnostic criteria

- Diagnosis of a given disease should follow guidelines developed by scientific societies and should include relevant symptoms, clinical examination findings, and other tests as appropriate (imaging, instrumental examinations, laboratory test, and so on).
- Criteria for diagnosis may be assigned a probability of presence of the disease based on progressive levels of evidence (e.g., not likely, possible, probable, very probable, near certain).

Diagnostic criteria

- “insufficient or not likely” may be conceptualized as a very small probability (e.g., 0 to 10%)
- “possible” may be conceptualized as a probability in the range 10-40%
- “probable” may be conceptualized as a probability in the range 40-60% (that is, the probability may be in favor of the disease, but also against it, so clinical judgment is required)
- “very probable” may be conceptualized as a probability in the range 60-90%
- “near certain” may be conceptualized as a very large probability (e.g., 90 to 100%)

Diagnostic criteria

- Symptoms should be distinguished from the findings of the clinical examination. If clinical examination maneuvers are an important element in diagnosis, it should be born in mind that small differences in how the maneuvers are conducted may produce very different findings.
- A peculiar issue linked to the diagnosis of occupational musculoskeletal diseases is the real objective character of the physical examination.
- Conventional medical wisdom assumes that the physical examination is an objective assessment: it is, but not always. Hearth sound assessed by a doctor are objective, in that they do not depend on the cooperation of the patient (and there are examples of physical examination findings, for example, in unconscious patients).

Diagnostic criteria

- With reference to the physical examination of patients with musculoskeletal complaints, the situation is different in that, if a few findings are really objective (e.g., circumference of an arm for evaluation of muscle wasting, or passive range of motion ignoring possible induced pain), most of the physical maneuvers recommended for the diagnosis of musculoskeletal diseases are in effect pain inducing maneuvers, that is, they rely upon the subjective response of the examined person (e.g., Tinel's or Lasegue's signs).
- As physical examination has been defined as "the process of evaluating objective anatomic findings through the use of observation, palpation, percussion, and auscultation" (Walker HK, Hall WD, Hurst JW (editors): Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. https://www.ncbi.nlm.nih.gov/books/NBK201/) a maneuver which rely upon the response of a subject may not be defined as really objective.

Diagnostic criteria

- Levels of evidence are critical in order to correctly frame the interpretation of the diagnosis since the minimum level of evidence is likely to vary depending on the actions to be taken.
- For example, the level of evidence may be different for the collection of national statistics than for the determination of financial compensation.
- For **insurance or civil litigation**, most systems require a minimum legal criterion of "**more likely than not**", which would correspond to a level in the range of "very probable" (or higher), whereas **for a criminal case** a fact should be assessed "**beyond any reasonable doubt**", which would correspond to a level of "**Near Certain**".
- The level of evidence is also likely to influence recommended treatments: for example, a **conservative treatment** may be recommended with a level of "**Possible**" while **surgery** may be recommended with a level of "**Very Probable**".

Example: diagnosis of shoulder tendinopathy

Diagnostic criteria	Level of evidence
Neck pain with palpation tenderness over the trapezius muscle.	Insufficient (may just be transient discomfort)
Shoulder pain worsened by abducting the upper arm.	Possible
Shoulder pain with clinical findings of palpation tenderness at the acromion and pain with active arm abduction greater than 45 degrees.	Probable
Symptoms, clinical findings and magnetic resonance imaging study that reports well described alterations of the tendon signal in the affected side and (if it is the case) absence of alterations in the asymptomatic shoulder.	Very Probable
Report of surgical intervention with documentation of tendon degeneration or laceration and histology demonstrating tendinosis.	Near Certain

Exposure assessment criteria

- The assessment of the workplace exposure to the presumptive risk factor(s) should be defined both qualitatively (ensure that the subject has actually been exposed to the factor) and quantitatively (ascertain the overall amount of exposure: e.g., level, frequency and cumulative duration).
- The evaluation of the exposure can be articulated for progressive levels of evidence both from the qualitative point of view (roughly: possible, probable, very probable, near certain) and from the quantitative point of view (by measures obtained by validated methods).
- If continuous personal measures are not available (e.g., total hours of exposure to a certain risk factor with a specific level), it will be necessary to define the exposure at least in a semiquantitative way, with reference to the levels that have been associated by the scientific literature with a significant risk of disease.

Example: exposure to biomechanical risk factors

Exposure assessment	Level of evidence
Exposure described by the worker or assumed based on a job title.	Insufficient
Administrative documentation of employment at a company, job title and some written documentation about the work from which it is possible to assume the exposure, at least qualitatively.	Possible
Written evaluation by a qualified professional who has observed the job and documented biomechanical exposures by means of an appropriate checklist or similar tool.	Probable
Video analysis with some measurements of risk factors at the job site (e.g., weight of tool or parts, estimation of postures, duty cycles, and so on).	Very Probable
Measurement of movements of the body or body parts of the worker by means of detailed video recordings and inertial measurement units, measurements of force exerted by means of mechanical sensors during the execution of the task and so on.	Near Certain

Criteria for attribution of an occupational disease

- Once the level of quality/probability of the disease diagnosis and the quality/probability of exposure are known, the occupational physician must combine this information into a statement about the relation of the disease to the occupation, taking into account all the available evidence, including the non-occupational risk factors present in a given worker, using information deriving by evidence-based review of the relevant scientific literature.
- An evidence-based review of the literature evaluating the relationship of workplace factors to disease should follow high quality methods. The review may include meta-analyses but should evaluate study quality issues such as bias and power.

Specific problems with musculoskeletal diseases

Specific problems with musculoskeletal diseases

- “One of the pitfalls in back pain research is that both back pain and its exposures can be simply assessed by a questionnaire. However, most of these measurements provide reliable and valid estimates of neither exposure nor outcome. In our view, this is one of the most important reasons for the continuing controversy about the causes of back pain, with some authors negating an association and others advocating important associations with work.” (Verbeek J, Burdorf A: National variations in back pain: ecological fallacy or cultural differences? Scand J Work Environ Health. 2014; 40: 1-3)

Specific problems with musculoskeletal diseases

- In other fields of occupational medicine (e.g., toxicology, cancer epidemiology) studies in which the disease has not been assessed and the exposure has not been measured according to current medical and scientific standard would be given no consideration.
- The same pitfalls about occupational musculoskeletal disease applies to occupational stress induced diseases, a field in which, mostly, neither diseases nor exposures are objectively defined.

Issues with studies about occupational diseases (musculoskeletal or stress induced)

- Some peculiar aspects distinguish the epidemiological setting from the clinical one as to musculoskeletal or stress induced diseases.
- The foremost issue is that **in the clinical setting it is the patient who seeks medical attention**, usually because of symptoms which are associated to discomfort, pain or functional limitation severe enough to rise the need to bring the own situation to a doctor's attention.
- Instead, **in the epidemiological** setting of a cross-sectional or cohort study, the situation is inverted: **it is the medical investigator who is looking for diseased persons** in what is an otherwise (assumed) healthy working population.

Issues with studies about some occupational diseases (musculoskeletal and stress induced)

- This situation affects indubitably the whole diagnostic process in different ways.
- Symptoms are not spontaneously presented to a doctor but “prospective” patients are specifically questioned to elicit the (eventual) presence of definite symptoms; in such setting it is well known the possible presence of serious biases due, for example, to the tendency of the subject to please the investigator (reporting what was requested), or various form of recall bias (and others…).

Issues with studies about occupational diseases (musculoskeletal or stress induced)

- The utility of physical examination (but even of instrumental tests) is drastically reduced by the low prevalence of the condition studied which affect the positive predictive value of tests with even high sensitivity or specificity.
- Expectations (even unconscious) of both the subject studied and the investigator may well impact the result of the investigation; the same may be true for the perceived utility of a “positive” study by the investigator (higher chance to publish) or by the diagnosis for the worker (compensation).

Criteria for attribution of an occupational disease

- The process of attributing the disease to the work activity requires first to establish the level of evidence of the diagnosis which, with reference to this specific point, should be preferably equivalent to “Very probable”.
- A level of evidence of “Probable” (where the probability in favor of the disease may be less than 50%) may be taken into consideration when constraints (available medical technology in a given place, a decision which must be made without the possibility to acquire other information) preclude the possibility of additional medical investigations.
- In this case, proper medical judgment of all the available evidence is warranted.

Criteria for attribution of an occupational disease

- Once that the level of evidence of the diagnosis is defined, it will be possible to proceed to the evaluation of the exposure which should be suitable for frequency, duration and level to cause the disease, in accordance with the evidence from the scientific literature.

- As in the case of diagnosis, the explicit definition of the levels of evidence on the basis of which it is decided to attribute a disease to a given work activity is essential to properly frame the relevant legal consequences.

Criteria for attribution of an occupational disease

- The quality of the exposure assessment has progressive levels of evidence: with reference to this specific point, the quality of the assessment of the exposure should be preferably equivalent to “Very probable”.
- A level of evidence of “Probable” (where the probability in favor of a good quality of the exposure assessment may be less than 50%) may be taken into consideration when constraints (available industrial hygiene technology in a given place, a decision which must be made without the possibility to acquire other information) preclude the possibility of additional workplace investigations.
- In this case, proper professional judgment of all the available evidence is warranted.

Criteria for attribution of an occupational disease

- The overall assessment of probability of an occupational disease needs to integrate the likelihood estimate of the disease with the estimated attributable contribution of the workplace exposure and the contribution of non-occupational factors.
- Few occupational diseases do not recognize established risk factors outside the work-environment (mostly, intoxications, mesothelioma …): for lung cancer, for example, tobacco smoking is the main risk factor and most musculoskeletal diseases, and psychological or psychiatric conditions are widely diffuse in the general population.
- As a result, occupational and non-occupational risk factors levels exert an inverse effect on the likelihood of a disease being caused by work.

Combining occupational and personal risk factors

Disease	Occupational risk	Non-occupational risk	Attribution to work
Insufficient	Insufficient	Indifferent	Ruled out
Possible	Possible	Dominant	Not likely
Probable	Probable	Average	To be evaluated based on the specific evidence available
Very Probable	Very Probable	Non dominant	Very Probable
Near certain	Near certain	Non dominant	Near certain

Criteria for attribution of an occupational disease

- The criteria proposed in this presentation may help the occupational physician in achieving a greater consistency in attributing diseases to occupational risk factors: in addition, they make the decisional process less opaque, offering the possibility to attribute a specific level of quality to the assessment of the disease and of the exposure and they also offer an explicit framework for attributing a specific disease to a workplace exposure, also taking into account nonoccupational factors which may be causally relevant.

Criteria for attribution of an occupational disease

- However, to advance the current knowledge about occupational diseases we need high-quality, cohort studies in which exposure and outcome are assessed objectively, with the best available appropriate techniques and confounders and possible sources of bias are fully controlled.
- These studies are the only ones which can provide accurate (enough) information to:
  - establish a reliable (enough) dose-effect relationship, which could form the basis for the causal attribution of diseases;
  - propose occupational exposure limits to prevent occupational diseases (and disorders, and, if possible, even discomfort).

“Facts do not cease to exist because they are ignored.”

Aldous Huxley