

Occupational Risk Factors for Carpal Tunnel Syndrome

Abstract

Work-related aspects of carpal tunnel syndrome (CTS) have engendered considerable research and debate resulting from its frequent occurrence in the population along with the cost of addressing it in the work place. Some studies have gone so far as to deny that CTS has any relation to work exposure, rather it largely results from predisposition of individuals. As such, the condition is non compensable leaving workers without any benefits due to their condition. This is despite the fact that high force and repetition of hand movements have been identified as CTS causes for years. As computer use has become endemic in recent years, several studies have concluded that the resulting exposures are insufficient to attribute any occupational causation to it. Rather, it is argued that genetic or worker pre-existing conditions are responsible for CTS development. This review analyses the existing literature to assess occupational carpal tunnel causation arising out of exposure to highly manual and repetitive jobs as well as intense exposure to keyboarding. We believe the literature supports a strong causal connection to carpal tunnel causation when exposed to highly repetitive and forceful jobs and a causal connection to keyboarding when the exposure dose is sufficient.

Keywords: Carpal tunnel syndrome; Musculoskeletal disorder; Odds ratio; Workers' comp; Repetition; Keyboarding

Review Article

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Abbreviations: CTS: Carpal Tunnel Syndrome; MSD: Musculoskeletal Disorder; OR: Odds Ratio; EDX: Electro Diagnostic; US: Ultra Sound; UE: Upper Extremity; BLS: Bureau of Labor Statistics; NIOSH: National Institute of Occupational Safety and Health; SNAP: Sensory Nerve Action Potentials

Introduction

Carpal tunnel syndrome (CTS) is a peripheral compression-induced neuropathy and currently the most frequently diagnosed upper extremity musculoskeletal disorder [1,2]. CTS is characterized by pain and paresthesia on the palmar-radial aspect of the hand. Risk factors for CTS are forceful use of the hand, repetitive motion, position of the hand, and vibration [3]. Interest in CTS persists because it is the most common upper level compressive neuropathy resulting in considerable cost to all parties, workers, employers, insurers and as such its etiology is often debated.

National prevalence of CTS among workers likely is between 3.1% [4] and 7.8% from the Upper Extremity Musculoskeletal Disorders study (UEMSD) [5]. The UEMSD study population consisted of participants from manufacturing and other hand-intensive jobs which may account for the higher prevalence rate. CTS as a work-related disorder has a significant monetary cost for industry and a leading cause of lengthy disability. The U.S. Bureau of Labor Statistics states that on average that there are 32 days of lost work for each CTS instance [6] while a Washington State Study (WSS) found that one-third of workers with CTS claims had more than 3 months of missed work [7]. CTS leads to more lost workdays than any other workplace injury. WSS found that

early surgical intervention appeared to have shortened disability duration for two-thirds of compensated workers.

However, workers' comp data may significantly underestimate the magnitude of the MSD problem as Bureau of Labor Statistics (BLS) are often much higher than comparable Workers' Comp data [8]. Under reporting of MSDs may be pervasive and a general phenomenon in US workplaces [9-18].

Despite the long history of CTS being classified as a work-related disorder, there remains a controversy regarding the etiology of CTS resulting from confounding factors that have lend some to dispute work-related exposure as an underlying factor for CTS [19]. CTS work-relatedness is confounded by a number of risks for median nerve pathology due to obesity, gender and age [20], rheumatoid arthritis, osteoarthritis, diabetes, previous wrist fractures [21], and hypothyroidism [22]. This has resulted in some investigators stating CTS is idiopathic, that is, arising spontaneously or from an obscure or unknown cause, and therefore non-compensable.

Critical review of the literature supports a work related causative mechanism for workers exposed to high force and repetition, confounding factors or not. However, there is an area of work exposure that has engendered extensive study with mixed attribution of causation, keyboarding or the use of video display terminals and of a 'mouse'. Cross sectional studies often rely on questionnaires to estimate exposures. These results in part because it has proven challenging to directly measure the forces and repetitions involved in occupations requiring computer data entry. Longitudinal studies account for employment duration

and hours of keyboard/mouse use per day resulting in a possible causal connection for CTS and keyboard/mouse use.

Diagnosis

While there is no gold-standard for establishing a diagnosis of CTS, there have been attempts to secure supportable conclusions for it. For example, a physical exam (PE) consisting of six criteria for CTS (numbness in the median nerve distribution, nocturnal numbness, weakness/atrophy of the thenar musculature, Tinel's sign, Phalen's test, loss of 2-point discrimination) were used to develop a model (VAS) that predicted the probability of CTS [23]. The probability of CTS for each case history predicted by the model then was compared with the probability of CTS independently assigned to each case by the clinicians using the VAS. The correlation between the probability of CTS predicted by the model and that estimated by the clinical experts was 0.71.

Despite this and other efforts to improve CTS diagnosis, it remains a clinical diagnosis based on patient symptoms and PE with the role of diagnostic testing still debated. When surgery is indicated clinically it is recommended that electro diagnosis (EDX) be performed [24]. This results in an expectation that EDX is valid though the available evidence does not bear it out in all cases [23,25]. EDX results have been questioned based on: 1) results are abnormal only when compression is severe enough to structurally alter the median nerve; 2) the assumption about what is an abnormal conduction velocity is challenged by the conduction velocities found in the asymptomatic population being skewed to the lower velocities; and 3) a highly variable cut-off point for determining abnormality [26]. Overreliance on EDX could result in withholding treatment even when there is a clear 'clinical' criterion for CTS.

Because EDX is uncomfortable for patients, time consuming and costly, ultrasound (US) is being increasingly used to diagnose CTS based on abnormal morphometry. US has a sensitivity of 89% and a specificity of 90% while EDX had a sensitivity of 89% and specificity of 80% as reported by Fowler et al. [27]. US were accurate in 89% of their cases while EDX was accurate in 86% of the cases. US have an additional advantage over EDX in that it provides morphological information regarding bifurcating median nerves, tumors and cysts.

Discussion

Controversy regarding CTS as a work-related disease

While most studies found significant correlation with work related activities, recently several studies concluded that CTS is not work related, rather it is idiopathic. For example, a review by Lozano-Calderón et al. [28] (L-CAR) assessed the role of occupational factors such as repetitive hand motion on the etiology of CTS and concluded that it is a minor factor and even debatable whether it is a factor at all [28]. Their review included a meta-analysis based on 117 articles that addressed either biological, occupational or both types of risk factors. Bradford-Hill [29] scoring system was used that employed a weighting scheme for the presence of nine epidemiological risk factors: plausibility, experiment, strength, biological gradient, consistency, specificity and independence, temporality, analogy, and coherence. Several

strong conclusions were: "in our opinion, the best quality studies of occupational factors did not support a relationship between occupational or repetitive activities and CTS" and "there is insufficient evidence to implicate hand use of any type, or typing in particular, as an important and direct cause of CTS, and to do so with confidence might be considered scientifically irresponsible".

In response to conclusions of the L_CAR review, McCabe [30] stated that "I don't think the evidence in this article supports such a strong statement [30]." He challenged several conclusions of the article based on the fact that the criteria of Hill are not current and should not be accepted without reservation. He further states that it is not clear whether the authors invented the measurement scale used in their article and hence the validity of the scoring system is questionable. In L-CAR it was also stated that "it can be argued that the diagnosis of CTS on the basis of symptoms and signs alone is pseudoscientific because it cannot be verified or falsified on the basis of reproducible objective testing." McCabe [30] noted that CTS is diagnosed on the basis of history and physical examination with high degree of accuracy and further states that "it cannot be argued that this is without scientific basis as written by the authors."

There are important considerations in Bradford-Hill 'criteria' employed in the L-CAR review that are often ignored. Phillips and Goodman point out that Hill never used the term criteria and stated that he did not believe any hard and fast rules of evidence could be laid down, emphasizing that his nine "viewpoints" were neither necessary nor sufficient for causation [31]. Further, "Hill's list seems to have been a useful contribution to a young science that surely needed systematic thinking, but it long since should have been relegated to part of the historical foundation, as an early rough cut." Hill warned that one should not mistake statistical precision for validity and that all scientific work is incomplete- whether it is observational or experimental. Phillips and Goodman concluded that "the uncritical repetition of Hill's causal criteria" is probably counterproductive in promoting a sophisticated understanding of causal inference."

Another review of Hill's criteria offers an insight into possible caveats in L-CAR's meta-analysis [32]: 1) Strength: Hill acknowledged that an association can be weak but it does not rule out a causal connection. 2) Consistency. Lack of consistency does not rule out a causal connection because some effects are produced by their causes only under unusual circumstances. 3) Specificity: requires that a cause leads to a single effect. However, causes of a given effect cannot be expected to lack all other effects. 4) Temporality: It is agreed that Cause must precede Disease. However, this does not mean that if D precedes C that the hypothesis that C can cause D is false. The observation is true only in this instance. 5) biological gradient: implies a unidirectional monotonic dose-response curve. However, a monotonic association is neither necessary nor sufficient for a causal relation. A non monotonic relation only refutes causal relations that require a monotonic dose-response curve. 6) Plausibility this is an important concern but it is far from objective or absolute. 7) Coherence: conflicting information may refute a hypothesis; however, conflicting information may be mistaken or misinterpreted. 8) Experimental evidence. Hill did not define what he meant by this. Experimental evidence is not a criterion

but rather a test of the causal hypothesis. A test may not be available in most circumstances. 9) Analogy: analogy provides alternate hypothesis. Absence of analogy goes only reflects lack of imagination or experience, no effect on the hypothesis.

Note that the causal origin of CTS in workers in an environment where they are exposed to high force requirements and 'very repetitive' activities was not examined in the L-CAR meta-analysis at all. This is despite of the existence of a long and enduring history of studies of upper-extremity neuropathies being associated with strenuous and high force activities going back over 100 years. When only repetitive hand use is considered, L-CAR reported 30 studies (66%) that found a correlation with CTS and 15 with no correlation. It would appear prudent to emphasize studies that did find a positive association. Finally, when studies that addressed the relation of vibration exposure and CTS were analyzed, 14 of 20 (70%) found correlation. Invoking L-CAR criteria, vibration is weakly plausible and therefore weakening the believability of any association.

Forceful-manual work increases the likelihood of CTS

Numerous studies and reviews address the relation of CTS to occupation. An early review in 1992 concluded that physical-work-load factors, such as repetitive and forceful gripping, are probably major risk factors for CTS and at least 50%, and as much as 90%, of all CTS cases in exposed populations appeared to be attributable to physical work load [33]. Recently, the timeline of two CTS reviews conducted in the 1990s was extended to January of 2005 after performing systematic searches of MEDLINE and EMBASE biomedical databases of peer reviewed studies [34]. Odds ratios (OR¹) with a 95% confidence interval for 38 primary research reports were calculated for each study along with the relative risk (RR) measure which approaches the odds ratio for rare diseases (i.e. OR ≈ RR because the relative risk of CTS is approximately 1 in 1000 in the general population). RRs ranged from 1 to 21 with significantly higher RRs associated with the use of hand-held vibratory tools, repetitive movements of the wrist and the duration of the exposure. Palmer et al. [34] stated "we found reasonable evidence that regular and prolonged use of hand-held vibratory tools increases the risk of CTS >2-fold" [34].

While there may be limitations some studies, available data supports a significant correlation between CTS and repetition, force and duration of the task. For example, a survey of several industries included videotaped job analysis that overcame a common criticism of studies relying on self-reporting was conducted by Silverstein et al. [35] in 1987 [35]. They reported associations of CTS with repetitive and forceful hand-wrist work with an OR of 2.7 in low force jobs and an OR of 15.5 in high-force jobs (hand force > 4 kg). In a pork processing plant where work exposure was documented by videotaping, epidemiological evidence indicated that some cases of CTS may be causally associated with work [36]. Combining electro diagnostic and clinical criteria for CTS classification in blue collar workers had a significant relative risk (RR) of 3 for women and a RR of 4.2 for men [37]. And in a Montreal Study of patients undergoing CTS surgery, 76% of CTS in male manual workers was judged attributable to work [38]. Similar conclusions of CTS work-relatedness were reached in several other studies [39-41].

In a carefully conducted cross-sectional study of 652 workers in 39 jobs, CTS was determined when there were: 1) Symptoms of pain, numbness, or tingling in the median nerve distribution of the hand. 2) Nocturnal exacerbation of symptoms. 3) Symptoms occurring more than 20 times or lasting more than 1 week in the previous year. 4) No history of acute traumatic onset of symptoms. 5) No history of rheumatoid arthritis. 6) Onset of symptoms since on the job. 7) PE: positive Phalen's or Tinel's sign; after ruling out cervical root, thoracic outlet, pronator teres syndromes. 8) EMGs were recorded [35]. Work exposures were estimated by a plant walk through by investigators to estimate cycle time, production rates, weight of parts handled. High repetitive jobs were defined as those with cycle times < 30 s and high force jobs as those with hand force requirements of more than 4 kg. Workers exposed to low forces were the comparison group. The study conclusion was that CTS was strongly associated with high force-high repetitive work and to a lesser extent with high repetition alone. Vibration also was a factor.

In a review of evidence for work-related CTS for 15 cross-sectional studies conducted between 1981 and 1991, only articles that had both symptoms and signs were considered and surgical release cases were included [33]. In each study prevalence and the attributable fraction (AF) = (OR - 1)/OR were determined where the AF is the proportion of exposed cases that would not have developed the disease in the absence of exposure. Review of 15 cross-sectional studies found a definite correlation between high force/repetition and CTS prevalence; 53% for butchers, 43% for some electricians, 25% for forestry workers, 14% for platers to 0.6% when job demands were considered low force and low repetition. AF = 0.97 for high force and high repetitiveness [e.g., Silverstein et al. [35] 1987]; for a typist AF = 0.74 [42]; and AF was at least 0.5 in 11 studies. The strength of association was generally high with the Odds Ratio > 10 for (1) high repetition and high force, (2) vibration exposure, and (3) occupation as a plater. It was concluded that exposure to physical work load factors, such as repetitive and forceful gripping, is probably a major risk factor for CTS in several types of worker populations. At least 50%, and as much as 90%, of all of the CTS cases in these exposed populations appeared to be attributable to physical work load.

An extensive review of work-related exposure published by the National Academies Press left little doubt that there is a strong relation between exposure and disabilities: the steering committee stated that [43].

"Restricting our focus to those studies involving the highest levels of exposure to biomechanical stressors of the upper extremity, neck, and back and those with the sharpest contrast in exposure among the study groups, the positive relationship between the occurrence of musculoskeletal disorders and the conduct of work is clear. The relevant studies have not precisely determined either the causal mechanical factors involved or the full clinical spectrum of the reported musculoskeletal disorders (which have often been lumped together nonspecifically as musculoskeletal disorders of a body region); nonetheless, those associations identified by the NIOSH review [44] as having strong evidence are well supported by competent research on heavily exposed populations. Examples include the excesses of musculoskeletal disorders of the upper extremities among

sawyers and auto assembly workers and the excesses of musculoskeletal disorders of the back among materials handlers and health care workers who lift patients.

There is compelling evidence from numerous studies that as the amount of biomechanical stress is reduced, the prevalence of musculoskeletal disorders at the affected body region is likewise reduced. This evidence provides further support for the relationship between these work activities and the occurrence of musculoskeletal disorders. “

In 2000, seven NIOSH-funded research groups formed the upper Extremity Musculoskeletal Disorders (UEMSD) Consortium to collaborate on studies of physical exposure and UE outcomes [4]. The motivation for the study was the fact that CTS was the most expensive upper-extremity musculoskeletal disorder at an estimated cost of \$2 billion annually with non-medical costs even greater [45]. All studies were prospective in design. Subjects were recruited from manufacturing, production, service, construction and healthcare. Hand diagrams and modified Katz scoring along with median nerve motor and sensory and ulnar nerve latencies across the wrist were collected. CTS case definition required both CTS hand symptoms and EDS results consistent with median nerve mono neuropathy at the wrist. Subjects meeting electrophysiological criteria for poly neuropathy at baseline were not included in the study. Prevalence was determined. Incidence analysis included all those at risk of becoming a new CTS case during the follow up.

In 2009 the data was pooled from 6 of the 7 studies. All study groups administered baseline questionnaires on demographics, medical history, psychosocial factors, work history, and musculoskeletal symptoms. The duration of each study ranged from 2-7 years. Symptom information was collected at regular intervals in all studies, though the length of intervals varied between one week and one year between studies. The number of follow-up symptom assessments collected from each subject ranged from 3-147 depending upon the frequency of questionnaires and duration of each follow-up. In five groups, EDS of the median and ulnar nerves of the wrist were collected along with UE physical examinations for all subjects at baseline. Six studies that included 4321 relatively young subjects with a mean age ranging from 30.8 to 43.4 years. After exclusions of prevalent CTS cases, 3515 workers were eligible for inclusion that resulted in an incidence rate of 2.3 cases per 100 years while varying between 0.7 to 5.6 cases per 100 years. The pooled symptom prevalence rate was 15.2% with a 7.8% prevalence rate for a cohort of mostly industrial workers. There was a 5.8% incidence rate in studies that required both symptoms and nerve conduction abnormalities. More of the workers in the pooled study were employed in jobs requiring hand-intensive activities than in two studies that denied correlation [46,47].

An overview in 2015 of systematic reviews and a meta-analysis of current research identified 10 Systematic reviews that covered 143 original studies [48]. The degree of overlap between the included systematic reviews was taken into account. Seven primary studies met criteria for inclusion of which 4 were longitudinal studies. The importance of including longitudinal studies is that they avoid the limitation of cross sectional studies being taken at only one instance in time. These studies provided

high quality evidence for risk factors such as repetition, force and combined exposures and moderate evidence for vibration exposure.

Studies conducted between 2000 and 2015 that concluded computer keyboarding is not a factor for CTS

A study of Professional Technicians: technical assistants (draftsmen) and machine technicians (technical drawing tasks, administrative and graphical tasks, and office based tasks) [49] concluded mouse and keyboard use were negatively correlated in all analysis and that it is unlikely that they can be considered an occupational risk for developing CTS. However, note in Table 3 of the article, when the heaviest keyboard use with >20hr/week was considered, the OR was 1.5 and an OR = 1.6 for median nerve symptoms based on a questionnaire. These OR values should have suggested to the authors that intensive and repetitive keyboard use could be a risk factor for CTS.

Imaging the median nerve after brief typing episodes did not find any correlate with typing in another study [50]. A review that whittled 4661 references down to eight epidemiological studies that met the inclusion criteria concluded that there was insufficient evidence for a causal relation between computer work and CTS [51].

An overview of systematic reviews in 2011 explored risk factors for upper extremity disorders among computer users while considering the effects of interventions [52]. Based on three reviews that covered 11 original studies, it was concluded that there was insufficient evidence for a causal relation between computer work and CTS.

A review and meta-analysis by Mediouni et al. [53] in 2014 concluded that it was impossible to show an association of CTS to computer work although some particular work circumstances may have an association [53]. However, the studies chosen for inclusion did not include any that support an association thereby assuring a weak association.

Another overview of systematic reviews and a meta-analysis of current research found on the basis of the highest quality study available that there is a significant relation between repetition and CTS. However, it was stated that the results of the meta-analysis demonstrate no association between compute use and CTS. The articles used to support this conclusion were the same articles used in the Mediouni et al. [53] study.

A meta-analysis of six studies that included five of the same studies used in several previous reviews also concluded no CTS -work association [54].

The Mayo computer study of work-related CTS: A study of computer users in a Mayo medical facility concluded that there was no difference in the frequency of CTS between computer users and the general population [55]. The result disputes the use of computers as a risk factor for CTS and suggests that the relation to musculoskeletal disorders is fuzzy at best. However, there are several aspects of the study that result in questioning its validity such as lacking a control group, only current workers were included in the study, which means ‘the survivor effect’ could be a factor and subject selection and exclusions were not

fully explained, exposure determination was not adequately quantified, and gender/age in comparison studies were not adequately controlled for. Therefore, it is possible that because of these methodological issues that this study should not be used to conclude whether there is a cause/effect of computer usage on the frequency of CTS. There has been a suggestion that there were severe methodological flaws in the study along with other questions [56]. Limitations (13 items) regarding this study are given in a WEB article [57].

Swedish CTS-keyboarding study: A study conducted in Sweden concluded that heavy keyboard use was beneficial in reducing the occurrence of CTS [1]. Questionnaires were sent to 2465 randomly selected individuals from the 'general' population of one region described as representative of the overall population of Sweden with 2003 respondents and 301 reporting hand numbness. A small sample of 123 individuals reporting no symptoms was used as the control. Persons reporting intensive >1 hr/day keyboard use were less frequently diagnosed as having CTS than those with little use, 2.4% for > 4hr/day, 2.9% for 1 to <4hr/day, 4.9% for 0 to <1hr/day and 5.2% for no keyboard use. Initially they had a >6hr/day category but never addressed this group separately. >1 hr/day was considered heavy use though it is typically considered light use. Nerve conduction studies (NCS) were performed routinely though it should be stated that CTS has been diagnosed in the absence of positive neurological results [58,59]. While NCS is often considered the gold standard for diagnosing CTS, test sensitivity is often in the 60-92% range, indicating a considerable number of positive cases can be missed [60-62].

A number of questions that arise with regard to this study are similar to those raised about the Mayo study [57]. Individuals with both keyboard and typing machine exposure were included which could confound the results. No breakout of the relative numbers was provided except N=1592 in their Table [57] versus the 2002 respondents. Subjects were not treated uniformly in that only 240 of 2003 that returned questionnaires underwent clinical examination and 219 of the 240 underwent nerve conduction studies.

The 4.2% percentage of CTS in the general population reported in Table [64] of their paper is substantially higher than the <1% typically reported in the general population is of some concern. Even more notable or suspect is the 5.2% CTS rate reported for the non-keyboard group. Reported prevalence rates for CTS vary significantly, in an industry wide study the rate was 0.174% [63] and in a U.S. study of 127 million workers a self-reported incidence of 1.47% of CTS with 0.53% for medically diagnosed CTS [64]. The difference between these prevalence rates and the Swedish studies raises questions and suggests major differences (e.g., age, gender, work environment, work attitude, exposure duration, etc.) between Swedish subjects and the U.S. population.

It is not clear how previous versus current exposure to keyboarding was addressed in this study. The survivor effect could be present, that is, only individuals that have better than average keyboarding experience remain in the pool. Those with symptoms (pain) remove themselves or are reassigned from keyboard work. The comparison populations were not comparable in that in the non-keyboard group 16% were professionals and

21% unemployed/retired while in the keyboard group 69% were professional and 12% were unemployed/retired. The work experience could have been substantially different for the two groups. They state that self-reporting keyboard time has limitations. Ideally one would like to monitor keystrokes over the course of several weeks/months without operator knowledge. An extensive discussion of the weaknesses of these studies of keyboard use can be found at a Cornell University Website [57].

Studies conducted between 2000 and 2015 that support work-related CTS due to computer use

Professional typists and work-related CTS: A problem in identifying keyboarding as a contributing factor to CTS is the amount and duration of exposure. Several studies that examined work style factors for computer professionals in India report that a large percentage, as high as 93%, of computer professionals report musculoskeletal discomfort [65-67]. Some individuals spent over 9 hr/day keyboarding. Hand/wrist problems were involved 19% of the time and Phalen's test for CTS was positive in 11.5% of the cases. Prevalence of CTS was found to be 13.1% for 648 subjects from 21 companies with CTS based on clinical diagnosis. Subjects with over 8 years of computer work had OR=3.3, over 12 Hours/day OR=4.9, and systems administrators had OR=2.5. These studies indicated that CTS is an important MSD among computer professionals.

The amount keyboard/mouse usage in the Mayo and Swedish studies was self-reported rather than an independent measure and all the subjects may not have been current users of computers. In contrast, a study of computer users in India may provide the strongest evidence of a causal effect of duration of computer use on the production of CTS [68]. Subjects (N = 648) were randomly selected from a computer complex where 7000 computer 'professionals' were employed. The selection criteria were that workers had to be continuously employed for at least 6 months as a computer professional immediately before selection for the study. They found an OR ratio of 1, 2.3 and 3.3 depending on years of computer work: <4, 4-8, and >8. 34% of workers with over 8 years of experience had CTS. OR as a function of hours of computer work showed the following results: OR= 1, 3.4, and 4.9 when working <8, 8-12, or >12 hours per day.

Why the discrepancy between the Mayo and Swedish studies and the above study in India? Clearly the Indian study focused on current computer professionals many of whom worked longer hours than those in the other studies. This subject population appropriately addressed the keyboarding - CTS relation. The workers were younger than those in the Swedish study suggesting if this study was followed up in a few years it is possible that an even larger effect would be found. Thomsen et al. [68] criticized the Indian study because there were no nerve conduction studies, however, clinical examinations were performed. In several respects, the Indian study was better controlled and studied a more appropriate subject group than used in the Swedish study [51]. This is by far the most focused study of computer use resulting in CTS [68]. While one can criticize aspects of the study design, the results speak for themselves and leave little doubt that heavy computer use can lead to CTS. Different populations may use computers in greatly different amounts (intensities)

which could contribute to the 'widely possibly wildly' different outcomes. Males had a higher prevalence of CTS than females likely resulting from the fact that they worked more years and for longer hours in the job than the females studied.

In a study of 100 bank workers in Turkey who worked more than 6 h per day for at least 2 years on a video display unit, upper extremity soft tissue disorders resulted from prolonged keyboard use, in particular [69], CTS was associated with cumulative time of computer use. Similar conclusions of work-related CTS for computer professionals among newspaper office workers in Mexico were found [70].

In 2012 a study of cumulative keyboard strokes among 461 government employees who had a work schedule of 7.5 hrs/day and underwent CTS surgery, 47.8% of those with lifetime cumulative strokes > 149.5 million were confirmed to have CTS with an OR of 2.4 and a relative risk of 2.6 [71]. 18.4% of those with lifetime cumulative strokes < 149.5 million were shown to have CTS. The mean number of strokes per year was 23 million. CTS increased significantly with increasing dose.

Similar studies did not address total keystrokes rather only time at the keyboard and were based on self-report. Because this is a cross sectional study it is not conclusive that the association between cumulative exposure and keyboard use is of a causative nature. However, it was concluded that there may be a possible association between cumulative exposure to keyboard strokes and the development of CTS among employees working in a data processing unit. Confounding factors were considered.

Computer keyboarding has been shown by ultrasound to result in increases in the cross sectional area (CSA) of the median nerve (MN) after typing 30 min [72]. These CSA increases could be related to compression of the nerve [73]. These MN changes suggest a possible link between CTS and keyboarding though clearly additional and longitudinal studies are warranted.

Musculoskeletal disorders among newspaper workers

using computers: Perhaps the more interesting aspect of the above contemporary studies in Sec 3.4.1 is that the results are congruent with those of an earlier study in 1994 [44]. It was a well planned and executed cross sectional study of 973 randomly selected employees in four departments (85% participation rate): editorial, circulation, classified advertising, and accounting was performed [44]. A self-administered NIOSH questionnaire was used to obtain demographics, upper extremity musculoskeletal symptoms, job tasks, work history, work organization and the psychosocial work environment. The case definition was previously developed by a NIOSH ergonomics medical team. The 1-year musculoskeletal disorder of the upper extremity (MSDUE) prevalence rate was 41%. Increased work load, time pressure, and greater hours of computer use were related to work-related MSDs, particularly for disorders in the hand or wrist area. For participants that reported typing 6-8hr/day the OR was 2.1 and those that typed more than 8 hrs/day the OR was 3.3. Prevalence rates were close to those previously reported which allayed any concerns with self-reporting.

The introduction of video display terminals into newspaper departments has been accompanied by a high prevalence of

musculoskeletal symptoms.

Four job evaluators that were blinded to case status observed three to five participants over the course of their work-shifts recording up to 30 observations per participant. An unconditional logistic regression analysis was used to develop models relating the predictor variables for three work-related MSDs in neck, shoulder, and hand/wrist. 395 of the 973 participants (41%) reported one of the three MSDs. Hand and wrist symptoms constituted 22% of the total MSDs. The risk of a hand or wrist MSD increased with the number of hours typing: typing 6-8 hours/day resulted in an OR of 2.1 versus the reference group that typed 0-2 hours/day. Those who typed more than 8 hours/day the OR was 3.3 versus the reference group. These results provide support for a dose response relation. These results are compatible with an earlier NIOSH study [74], a follow-up study [75] and a recent study [71] that found increased risk for newspaper editors using a PC (computer) frequently, intensively, and with more psychological demands.

Review articles between 2000 and 2015 that support work-related CTS due to computer use:

Several studies compared computer users with office workers that had little computer usage thereby including a more appropriate reference group than one that uses the general population. A meta-analysis of six studies yielded significant ORs with frequent mouse use (=1.93), frequent computer use (=1.89), and years of computer use (=1.92) [54]. The studies concluded that computer use might be a minor occupational risk factor for CTS. Evidence for work-related CTS resulting from forceful, angular, and repetitive hand use or with vibration was judged very strong [76]. There was weaker support for CTS in typists or data entry operators but may occur with intensive computer use of at least 12 to 20 hr/wk. The 12-20 hrs/wk is considerably less exposure than occurred in the Indian studies where a more definitive relation was apparent. Nevertheless, it was concluded that hours spent keying appears to be a risk factor for MSDs among computer users [49,68,71]. It was noted that the studies of Stevens [55], Thomsen [51] van Rijn [77] and Mediouni et al. [53] did not pursue sufficiently high exposures and therefore their evidence is regarded as insufficient to conclude whether typing results in CTS.

In a review of 11 studies of risk factors for MSDs among computer users, it was noted that 50,000 to 200,000 keystrokes per day may cause irritation to the membranes surrounding the extensor tendon synovial sheaths or the tendons themselves [78]. Loading of the flexor tendons causes an increase in carpal tunnel pressure. 10 of 11 studies that were reviewed agreed that exposures were the cause of the MSDs with significantly higher prevalence and incidence for the exposed groups relative to the referents.

In addition to the above there is considerable ergonomic literature that supports a strong relation between exposures and MSDs [79-83].

Cumulative keystrokes as a factor in CTS development

Cumulative keyboard strokes were calculated for four groups of government employees in data processing and data entry based on the use of the payroll registry in a cross sectional study [71].

Two cases were analyzed: 1) patients that had CTS surgery; 2) patients that had CTS surgery that were identified through clinical exam. Work schedule was 7.5 hours for 5 days per week. Four groups were formed based on exposure. The group with > 149.5 million cumulative strokes over years of employment had an OR = 2.41 in comparison to the low exposure group. A dose-response relationship between cumulative exposure to key-board strokes and CTS was found suggesting total keyboard strokes should be taken into account as an exposure measure. As in the Indian keyboard study, heavy keyboard use was identified as the critical factor in CTS development.

Among WRUEDs, CTS has the biggest impact in professional computer users their health and in industrial-related medical and non-medical costs [79]. From the 37,804 cases of CTS reported in 1994, 7897 (24%) were attributed to repetitive typing or keyboard data entry [3]. The loss in productivity is manifested before (less typing speed), during and after (days of hospitalization) the treatment of CTS. During typing, the causes for CTS are keystroke activation force, tactile and proprioceptive feedback, repetitiveness of the task [81], percentage of time typing, typing speed, the unequal distribution of finger usage, key switch make force and typing force [84]. Although typing does not lead to CTS due to the high force required [85], the elevated level of repetition makes it a major factor in CTS pathogenesis.

In 2015 an update of the NIOSH Quality of Work Life survey of MSD risk factors covering the 2000 year decade found that there is a relationship between MSDs and physical exposure variables [86]. In addition, psychosocial risk factors appear to influence outcomes and are being increasingly studied. Analysis performed in 2010 led to the conclusion that the overall pattern that workplace exposure to repetitive or forceful hand movements is associated with upper extremity disorders.

Clinical and basic science studies of median nerve pathology resulting from repetitive motions

Injuries of the wrist and hand are the most common regions in repetitive motion disorders that contribute to worker disability [87]. To address the underlying factors that result in CTS a rat model of repetitive motion disorders was developed. Rats were trained to perform a voluntary repetitive task to address anatomical and physiological changes in the median nerve. The task reflected postural and work pace demands derived from the epidemiological literature. Both anatomical and physiological signs of progressive tissue damage were present in the model. Over 3-12 weeks of task performance there were increased numbers of macrophages in both limbs, signs of fibrosis and a slight though significant slowing of the neural conduction velocity in the median nerve. Study results indicated work-related CTS developed through mechanisms that include injury, fibrosis, and subsequent nerve compression.

A study found blood flow in rat sciatic nerve was reduced by 50% with a strain (stretch) of 11% and as much as 100% with a strain of 15.7% [88]. There was minimal recovery of blood flow after only a 15% strain suggesting that long term nerve damage is possible. Nerve conduction amplitudes were also reduced by as much as 70% after a 6% strain. Aged rats

performing a repetitive task exhibited sensorimotor declines that were associated with decreased median nerve conduction, and increased pro-inflammatory cytokines in the median nerve and cervical spinal cord neurons [89]. In addition to peripheral nerve damage there were spinal cord neuronal alterations that raise another consideration of the long term effects of repetitive movements. Additional evidence for nerve damage resulting from experimentally induced stress consisted of deformations, ischemia, and decreased axonal transport in several studies that include 100's of references to related studies [90-92].

On the basis of biomechanical and histological findings, it has been speculated that insult to the synovium and the flexor tendons due to aging or repetitive and forceful movement of the wrist and fingers could lead to degeneration of the synovium and the tendons, in turn leading to enlargement of the carpal tunnel from the inner side. Thus, the volume of the carpal tunnel contents increases, leading to median nerve compression and eventually the idiopathic carpal tunnel syndrome [93].

In a study of computer keyboarding biomechanics and acute changes in median nerve indicative of carpal tunnel syndrome cross-sectional area and swelling ratio increased after 30 and 60 min of typing, and then decreased to baseline after 30 min of rest [72]. Peak ulnar deviation contributed to changes in cross-sectional area after 30 min of typing. Results from this study confirmed a typing task causes changes in the median nerve, and changes are influenced by level of ulnar deviation. Furthermore, changes in the median nerve are present until cessation of the activity. While it is unclear if these changes lead to long-term symptoms or nerve injury, their existence adds to the evidence of a possible link between carpal tunnel syndrome and keyboarding. While these changes may be part of a normal physiologic process, they also might represent part of the pathomechanics that leads to CTS. Further studies including individuals with CTS and following subjects longitudinally are needed.

Repetitive microtrauma or overuse injuries that often affect upper extremities were studied in long term use of computers [94]. Sensory nerve conduction velocities (SNCV) for median, radial and ulnar nerves in the wrist of computer users with the same parameters in controls who do not use computers regularly were measured. Computer users had a tendency toward developing median and ulnar sensory nerve damage in the wrist region. Mechanism of delayed SNCV in the median and ulnar nerves may be due to sustained extension and ulnar deviation of the wrist during computer mouse use and typing.

Carpal tunnel pressures resulting from computer mouse use were significantly greater during dragging and pointing tasks than when resting the hand (static posture) on the mouse ($p = 0.003$) [95]. The mean pressures during the dragging tasks were 28.8 ± 33.1 mmHg, ~12 mmHg greater than the static postures. In many participants the carpal tunnel pressures measured during mouse use were greater than pressures known to alter nerve function and structure, indicating that jobs with long periods of intensive mouse use may be at an increased risk of median mononeuropathy [96].

Questions have been raised regarding the appropriateness of mice or rat models used to test hypothesis regarding human

work-related exposures. Old world monkeys which are closer genetically than mice to humans were used to investigate changes in median sensory nerve conduction velocity (SNCV) over several weeks of exposure to a voluntary, moderately forceful, repetitive pinching task performed for food rewards by a small sample of young adult female monkeys (*Macaca fascicularis*) [97]. SNCV which was derived from peak latency decreased significantly in the working hands of three of the four subjects. The overall decline in NCV was 25%-31% from baseline. There was no decrease in SNCV in the contralateral, nonworking hands. This new animal model demonstrates a temporally unambiguous relationship between exposure to a moderately forceful, repetitive manual task and development of median mononeuropathy at the wrist, and recovery of SNCV following termination of task exposure. This study contributes to the pattern of evidence of a causal relationship between manual work, median mononeuropathy, and carpal tunnel syndrome in humans.

In concert, these studies in rats, monkeys, and humans demonstrate convincingly that repetitive hand use results in median nerve alterations that can result in CTS. Nerves subjected to a sufficient number of repetitions will develop pathological changes that could result in work-related performance deficits.

CTS and genetic factors

Peripheral neuropathy is a common complication of amyloidosis with CTS frequently present. CTS can be an early symptom in hemodialysis-related amyloidosis, primary systemic AL amyloidosis, senile systemic amyloidosis (SSA) and transtretin (TTR) derived amyloid polyneuropathy. It is a rare disease with Mayo Clinic estimating less than 3000 people in the United States [98]. Nevertheless it is used to argue that CTS is more often than not idiopathic. It was diagnosed in 1939 by Andrade [99] as a disease that attacks many members of a family but the families in which it occurs have no genetic relationship. It results in severe destructive process in nerve myelin sheaths and results in the degeneration of the nerve fibers. It was noted to occur in higher percentages in old men [100]. Genetic amyloidosis begins in the 5th decade of life and often CTS is first noticed [101]. An early genetic link was identified in 1965 when 11 families suffered from amyloid polyneuropathy while all denied any relationship among the families. However, a genealogical study demonstrated common ancestry of all 11 kindreds in a couple married about 1775. 146 persons in 7 generations were affected.

SSA has been indicated in 25% of people over 80 yrs in one study [102]. SSA appears to be very rare in the Japanese population while transthyretin Val30Met familial amyloid polyneuropathy is more prevalent in Japan [103]. Two forms of FAP ATTR Val30 Met correspond to an early onset group (<50 years) and late-onset group (>65). Nerve damage specific to the CT entrapment site is less significant in patients with this disease.

Between 8-18% of individuals with CTS that have normal nerve conduction measures and minimal demyelination suggesting that CTS is not primarily a neuropathy [104]. It has been suggested that genetic factors are associated with CTS [28,105,106]. Another example of a genetic linkage is that COL5A1 and BCN gene-gene interactions modulate the risk of CTS in females. There are likely

multiple genetic variants associated with the risk of CTS [107]. However, it is very early in the genetic-CTS link and therefore additional studies are required to extend and replicate the current findings.

Multifactorial nature of CTS etiology

There remains a controversy regarding the etiology of CTS. Work-related exposure has been disputed as an underlying factor by a number of studies. Work-related aspects are confounded by a number of risks for median nerve pathology due to obesity, gender and age [20], rheumatoid arthritis, osteoarthritis, diabetes, previous wrist fractures [21], hypothyroidism [22], female gender, obesity, and age [20]. Nerve alterations can result from compressive forces due to prolonged or abnormal postures for extended durations that result in increased pressure around the nerve. The median nerve is well vascularized and therefore can be compromised by stretching and compression that may trigger an inflammatory process which then results in swelling and impairment of the blood supply. Normal gliding movement of the nerve is impaired. Swelling, inflammation, reduced micro-circulation and impaired gliding lead to nerve fiber dysfunction [108].

In reviewing data largely before 2004, it should be apparent that different conclusions regarding work place exposure and CTS have been obtained even after a long history of a relationship. In a critical review by the U.S. Department of Health and Human Services [109] it was concluded that "there is evidence for a positive association between force and CTS based on currently available epidemiological data." Further, "there is evidence for a positive association between jobs with exposure to vibration and CTS. There is also strong evidence for a relationship between exposure to a combination of factors (e.g., force and repetition, force, and posture) and CTS."

Why are there contradictions in the literature regarding work exposure as causal for CTS? Some may be due to the underlying motivation of the various reporting and supporting parties such as insurance companies and industrial entities. Others are likely legitimate varying outcomes based on gender, genetics, societal pressures, worker expectations, the type/range of work exposure, etc. However, when 'apples and oranges' comparisons are avoided, and a focus is on large force/vibration exposures, or very high repetitions there appears to be no controversy as to whether CTS will be found in a significant number of the workers so exposed. Work-related CTS is a clinically recognized upper level MSD in many countries for many years.

In 1998 the National Research Council organized a steering committee to review evidence for work-related musculoskeletal disorders [110]. After careful consideration, they chose not to have the presentations focus on specific parts of the body and associated musculoskeletal disorders. Workshop discussions elucidated the following sets of relationships between factors that potentially contribute to musculoskeletal disorders: (1) biological responses of tissues (muscles, tendons, and nerves) to biomechanical stressors; (2) biomechanics of work stressors, considering both work and individual factors, as well as internal loads; (3) epidemiological perspectives on the contributions

of physical factors; (4) non-biomechanical (e.g., psychological, organizational, social) factors; and (5) interventions to prevent or mitigate musculoskeletal disorders, considering the range of potentially influential factors. It was intended that this would provide a framework for reviewing the science base for each set of relationships, as well as the wider interactions among the sets. This approach allowed taking advantage of both basic and applied science and a variety of methodologies, ranging from tightly controlled laboratory studies to field observations. Sources of evidence that extended well beyond those provided by the epidemiological literature were also considered.

The steering committee explored the complex problem of musculoskeletal disorders in the workplace. They supplemented their professional expertise with workshop presentations, commissioned papers and other submissions, and discussions with invited workshop participants. They found very clear signals on some topics and weaker signals on others-but little in the way of contradiction. While there are many points that require further study, they have confidence in the thrust of the workshop conclusions, which draw on converging results from many disciplines, using many methods:

There is a higher incidence of reported pain, injury, loss of work, and disability among individuals who are employed in occupations where there is a high level of exposure to physical loading than for those employed in occupations with lower levels of exposure.

There is a strong biological plausibility to the relationship between the incidence of musculoskeletal disorders and the causative exposure factors in high-exposure occupational settings.

A series of presentations and discussions led the National Institute of Occupational Safety and Health (NIOSH) to the following summary of the scientific evidence for work-related MSDs [109]:

Strong associations between measured biomechanical stressors at work and musculoskeletal disorders were observed in most studies; however, temporal contiguity between the stressors and onset of effects, as well as evidence of amelioration after reduction of stressors could not always be established, nor could the clinical course of the observed effects. This shortcoming, though inherent to practical requirements of such research, makes it difficult to make strong causal inferences on the basis of the evidence from any individual study. Nevertheless, the steering committee reached the following three conclusions:

Restricting our focus to those studies involving the highest levels of exposure to biomechanical stressors of the upper extremity, neck, and back and those with the sharpest contrast in exposure among the study groups, the positive relationship between the occurrence of musculoskeletal disorders and the conduct of work is clear. The relevant studies have not precisely determined the causal mechanical factors involved nor the full clinical spectrum of the reported musculoskeletal disorders (which have often been lumped together non-specifically as musculoskeletal disorders of a body region); nonetheless, those associations identified by the

NIOSH review as having strong evidence are well supported by competent research on heavily exposed populations. Examples include the excesses of musculoskeletal disorders of the upper extremities among sawyers and auto assembly workers and the excesses of musculoskeletal disorders of the back among materials handlers and health care workers who lift patients.

- I. There is compelling evidence from numerous studies that as the amount of biomechanical stress is reduced, the prevalence of musculoskeletal disorders at the affected body region is likewise reduced. This evidence provides further support for the relationship between these work activities and the occurrence of musculoskeletal disorders.
- II. Evidence of a role for biomechanical stress in the occurrence of musculoskeletal disorders among populations exposed to low levels of biomechanical stressors remains less definitive, though there are some high-quality studies suggesting causal associations that should serve as the basis for further investigation. In cases of low levels of biomechanical stress, the possible contribution of other factors to musculoskeletal disorders is important to consider.

Basic science studies of median nerve pathology

Because CTS results from compression of the median nerve and resulting pathology, its study is critical. While directly assessing nerve damage in humans has limitations and ethical concerns, animal experiments provide an alternative to address nerve damage that results from exposures that substitute for "work-related exposures". After up to 400 hours of vibration in a rat model, neurophysiological and histological changes were observed in the nerve that were best described as severe degenerative changes in axons [111]. When the hind legs of adult rats were exposed for 4 hrs for 5 consecutive days, nerve damage was found in unmyelinated nerve fibers characterized as deranged axoplasmic structure [112]. Repetitive motion disorders were studied using trained rats to perform a voluntary repetitive task [87]. Both anatomical and physiological signs of progressive tissue damage were present in the model. Over 3-12 weeks of task performance there were increased numbers of macrophages in both limbs, signs of fibrosis and a slight though significant slowing of the neural conduction velocity in the median nerve. The study results indicated work-related CTS developed through mechanisms that include injury, fibrosis, and subsequent nerve compression.

In a recent attempt to determine whether proposed International Standards regarding frequency weighting for vibration exposure for frequencies > 100 Hz, vascular changes indicative of dysfunction were found [113]. After rabbit tibial nerve was compressed for 2 hours, intravital stains were used to observe the effect of graded compression on blood flow [114]. Nerves observed 3 or 7 days after compression showed no or very slow blood flow indicating acute compression of a nerve may result in persistent impairment of intraneural microcirculation. These studies indicate that repetition and compression can result in physiological damage of a nerve.

Despite the difficulty of the study of median nerve damage in humans there have been several attempts. Sensory nerve action potentials (SNAP) were used to measure the effects of focal neural compression of the median nerve in patients with and without CTS [115]. Numbness and paresthesia increased during the application of nerve compression. SNAP amplitudes decreased and superexcitability increased more in patients with CTS compared to controls indicating impaired axonal functioning. Paresthesia appears to be the most common result of median nerve impairment [116]. Chronic nerve compression can occur due to repetition, awkward postures, excessive force and vibration and may contribute to the development of chronic nerve compression [115,117]. Increased pressure in the carpal tunnel has been found in patients with CTS [118,119].

Underreporting of MSDs

Negative worker -insurer interactions include: not being listened to; physician not understanding full impact of injury on worker, unjustified denial of claim, sending worker to multiple IME, sending worker to IME out of town, questioning legitimacy, stigma, not being believed. Physician unprofessional behavior or lack of knowledge of the injured system and either avoiding responsibility or making a rash decision. Administrative deficits can include, absent or incorrect information, cost containment via service approval, unclear written communication, limiting contact with the physician. The worker is subject to the power imbalance with the system, prolonged claims and appeals processes, medical reports being used out of context, and a general lack of knowledge about rights. Claims can be manipulated by ignoring or contesting diagnoses, using confusing jargon and legalistic communication, slow payments to non-preferred physician to discourage treatment [8-17,120-123].

In a Special Issue of the American Journal of Industrial Medicine, an article by Spieler & Burton [124] in 2012 titled "The lack of correspondence between work-related disability and receipt of workers' compensation benefits" [124]. They reported that many workers with work related disabilities do not receive workers' compensation benefits in part due to increasingly restrictive state workers' compensation programs. Higher standards of proof lead to denial of claims. When there are only population based studies it is nearly impossible to meet the higher standard. Disability caused by work is common and fewer claims are being paid due to the growing barriers to obtaining benefits. This indicates that has been little abuse of worker's comp by workers to date rather it is more likely that the system often disadvantages workers.

Conclusion

Work-related injury is a major public health problem that involves workers, their families, friends, colleagues and the wider community. Insurer-worker Interactions are often negative resulting in considerable psychosocial consequences. Involvement in compensation systems contributes to poorer outcomes for claimants [125]. Insurers control the acceptance of

claims, financial support, medical services, as well as negotiation of compensation. While worker's comp was intended to be a no fault system, it often fails the injured worker.

Presently there is inadequate exposure assessment for the physical or work organization factors and failure to disentangle the effects of the two sets of variables on musculoskeletal outcomes. Known physical stressors include repetitive and sustained exertions, forces, posture stresses, work duration, contact stresses, vibration, and low temperatures. Keyboarding remains controversial due to inadequate ergonomics of many studies. Mild exposures in some keyboarding studies could be considered part of a company's wellness program for employees. However, when a very high number of keyboard strokes are experienced there is a high rate of CTS. Clearly future research is needed to develop standard methods of quantifying exposures in a variety of work environments. Dose-response relations between physical stressors and medical outcomes need to be developed if conflicts regarding culpability are to be resolved.

Based on the epidemiologic studies noted above, especially those with quantitative evaluation of repetitive work, the strength of association between CTS and repetitive movements is significant as measured by OR ranges between 2 and 15. Higher ORs were found when contrasting highly repetitive jobs to low repetitive jobs, and also when repetition occurred in combination with high levels of forceful exertion. There is strong evidence of a positive association between highly repetitive work alone including keyboarding and CTS. Individual studies that are referenced here along with a consensus of several comprehensive national reviews provide strong evidence for CTS development resulting from excessive force, high repetitions, or their combination in the workplace.

The question "Is carpal tunnel syndrome work-related or idiopathic?" has been answered; it can be either and both. In Science, a single study with either a positive or negative outcome should be viewed as a "miracle". This is not the case for work-relatedness of CTS as shown here with numerous clinical and basic science studies, systematic reviews and overviews supporting a positive association. The next logical step in evaluating work-related CTS is a global review (a review of a review of a review) of overviews (a review of reviews) of systematic reviews of original studies.^{1,21}

1 Odds Ratio (OR) is the probability of CTS in one population divided by the probability of no CTS in another population. With very low probabilities, a few out of a thousand, OR is essentially the ratio of the rates observed in two populations, e.g., CTS in workers at 3/1000 and 1/1000 in the general population then OR=3 with an inconsequential error.
Sensitivity = number of true positives / (number of true positives + the number of false positives).

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