Achtergronddocument

Bij registratierichtlijn N613 Carpale Tunnel Syndroom

Cascode: N613
ICD-10-code: G56.0

Nederlands Centrum voor Beroepsziekten

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Bij registratierichtlijn N613 Carpale Tunnel Syndroom

Cascode: **N613**
ICD-10-code: **G56.0**

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Dit achtergronddocument bij de registratierichtlijn wordt beschreven aan de hand van het 6-stappenplan voor het melden van beroepsziekten bij het Nederlands Centrum voor Beroepsziekten (NCvB).

Het 6-stappenplan van het NCvB luidt:

Stap 1. Vaststellen van de aandoening/ziekte
Stap 2. Vaststellen van de relatie met werk
Stap 3. Vaststellen van de aard en het niveau van de oorzakelijke blootstelling
Stap 4. Nagaan van andere mogelijke oorzaken en de rol van de individuele gevoeligheid
Stap 5. Concluderen en melden
Stap 6. Preventieve maatregelen en interventies inzetten en evalueren

Naast de informatie die is beschreven in de registratierichtlijn bevat dit achtergronddocument ook de referenties naar de medische literatuur die is gebruikt.

Inleiding
Het Carpale Tunnel Syndroom (CTS) ontstaat doordat de nervus medianus knel zit in de buurt van de pols, in de carpale tunnel. Deze tunnel is een doorgang voor zenuwen en pezen die van de onderarm naar de hand lopen. De klachten zijn: tintelingen, pijn en een doof gevoel in de hand en vingers. Het gaat dan om de duim, wijsvinger, middelvinger en ringvinger. Patiënten kunnen ook minder kracht hebben in hun hand. De klachten komen vaak 's nachts of vroeg in de ochtend voor. Patiënten hebben de klachten ook regelmatig in allebei hun handen (Nederlandse vereniging voor Neurologie). CTS is een veelvoorkomende aandoening bij volwassenen, met een prevalentie van ongeveer 6% in de algemene populatie en een incidentie van ongeveer 0,2% (Federatie Medisch Specialisten). De prevalentie is aanmerkelijk hoger in aanwezigheid van systemische aandoeningen, zoals diabetes, hypothyreoïdie en reuma. CTS komt vaker voor bij vrouwen dan bij mannen. Hoewel de aandoening zelden aanleiding geeft tot ernstige invaliditeit kan het syndroom wel aanleiding geven tot hinderlijke pijnklachten en sensibele en motorische veranderingen in de hand, met een negatief effect op de kwaliteit van leven, door onder andere verstoring van werk en slaap. (Federatie Medisch Specialisten).

Stap 1. Vaststellen van de aandoening

De werkgroep van de Federatie van Medisch Specialisten (2017) is van mening dat de diagnose 'klassiek CTS' kan worden gesteld als er bij iemand sprake is van de volgende vijf kenmerken (in overeenstemming met de richtlijnen van het Nederlands Huisartsen Genootschap, de American Academy of Neurology en de American Academy of Orthopedic Surgeons):

1. een volwassen patiënt;
2. met tintelingen, al dan niet met pijn en een doof gevoel, in het verdelingsgebied van de n. medianus;
3. waar de patiënt 's nachts wakker van wordt;
4. met klachten die erger worden of juist verminderen door bepaalde houdingen of bewegingen van de hand en pols;
5. waarbij er op basis van anamnese en lichamelijk onderzoek geen aanwijzingen zijn dat er sprake is van een andere oorzaak.

Er is bij het CTS sprake van een syndroomdiagnose, er is geen universele consensus met betrekking tot de gevalsdefinitie en er is geen gouden diagnostische referentie-standaard voor de diagnose. Diagnostische tests zoals vragenlijsten, handdiagrammen, zenuwgeleidingsonderzoek en provocatietesten zijn volgens de richtlijnen niet nodig om de diagnose te stellen.

Stap 2. Vaststellen van de relatie met werk

De drie criteria die experts hanteren om de relatie met werk vast te stellen van een ziekte of aandoening zijn de grootte van de bewezen risicofactoren uit de medische literatuur, een tijdsrelatie en de biologische plausibiliteit (Verbeek 2012). Voor *een groep werknemers* met een bepaalde blootstelling of een bepaalde beroepsgroep wordt een ziekte of aandoening veelal aangemerkt als beroepsziekte als de etiologische fractie door risico's in het werk groter dan 50% is. Het relatief risico is dan twee of groter. Een etiologische fractie van 50% impliceert dat onder de zieke blootgestelde werknemers 50% van de ziekten te wijten is aan de blootstelling. Voor *een individuele werknemer* dient de bedrijfsarts te bepalen of de tenniselleboog bij de werknemer in overwegende mate wordt veroorzaakt door het werk op basis van op *groepsniveau* verkregen evidence-based risicofactoren. Bij het vaststellen of er een oorzakelijk verband met het verrichte werk kan zijn bij een werknemer, is zoals gezegd ook de tijdsrelatie van belang (bijvoorbeeld de ziekte is ontstaan nadat met het huidige werk is begonnen, de symptomen verergeren bij specifieke taken of na drukke perioden, of de klachten zijn minder na vrije dagen, na een vakantie of na de invoering van preventieve maatregelen) en of de risicofactor in het werk ook in lijn is met het veronderstelde pathofysiologische mechanisme voor de aandoening of ziekte, denk bijvoorbeeld aan een voldoende latentieperiode of blootstellingsduur of 'overbelasting van bepaalde structuren zonder voldoende herstel'.

Stap 3. Vaststellen van aard en niveau van de oorzakelijke blootstelling

De werkgerelateerde risicofactoren voor CTS zijn gebaseerd op een systematische literatuurstudie met meta-analyse en GRADE uitgevoerd door het Nederlands Centrum voor

Beroepsziekten. De resultaten zijn gepubliceerd in het 'peer-reviewed' tijdschrift Health Science Reports en dit artikel staat in de bijlage I (Hassan e.a. 2022) en is hier digitaal te vinden: Work-relatedness of carpal tunnel syndrome: Systematic review including meta-analysis and GRADE - Hassan - 2022 - Health Science Reports - Wiley Online Library. Uit dit artikel blijkt dat er vier werkgerelateerde risicofactoren met sterk bewijs voor CTS zijn (zie figuur 2 over de werkgerelateerde risicofactoren en tabel @3 over de definitie van hoge en lage blootstelling):
De vier werkgerelateerde risicofactoren met sterk bewijs voor CTS zijn:

- De Strain Index ≥ 6,1
- Hoge mate van handkracht ≥ 4 op de Borg-10 schaal ('pittig'-'zwaar')
- Een blootstelling hoger dan de Hand Activity Level score van de ACGIH
- Sterk repeterend werk met een Hand Activity Level score ≥ 5

De Strain Index is een meet- en rekenmethode die bestaat uit drie kwantitatieve variabelen: 1) duur van de inspanning, 2) aantal inspanningen en 3) duur van een taak per dag, en drie kwalitatieve variabelen die berusten op een expertoordeel: 1) intensiteit van de inspanning, 2) hand/polshouding, en 3) snelheid van werken. In de bijlage bij deze registratierichtlijn en in het achtergronddocument staat een voorbeeld van het scoreformulier inclusief een link naar een excelbestand.

De Hand Activity Level score van de ACGIH is een Amerikaanse methode die het risico op overbelasting van de hand en pols beoordeelt. Voor meer uitleg zie een Engelstalige en Nederlandse uitleg. De methode richt zich specifiek op CTS en tendinopathieën aan de pols. De evaluatie is gebaseerd op de handbewegingen en de handkracht gedurende een kortcyclische taak, gedurende minstens 4 uur per dag. Deze methode combineert twee parameters: handactiviteit en handkracht. De handactiviteit wordt uitgedrukt op een schaal van 0 tot 10 (VAS schaal). Daarbij staat 0 voor geen activiteit en 10 voor de hoogst denkbare activiteit. Het is een kwalitatieve beoordeling die de duur en de frequentie combineert. De handkracht wordt uitgedrukt als percentage van de maximale kracht, normalized peak force (NPF). Dit kan op drie manieren: de Borg schaal, de Moore-Garg schaal of als percentage van de maximale vrijwillige contractie (%MVC) na het meten van de spieractiviteit (EMG). De meest gebruikte werkwijze is de Borgschaal. De operator geeft dan aan hoeveel kracht hij dient uit te oefenen. De risicoscore kan men aflezen in een grafiek. Deze duidt de relatie tussen de handkracht en handactiviteit aan. Er is een actiewaarde (AL) en een grenswaarde (TLV).

Let op 1: Het is mogelijk aan te bevelen om de werkplekbeoordeling uit te laten voeren door een ergonoom, arbeidshygiënist of bedrijfsfysio- of –oefentherapeut met ervaring met één of meerdere van de methoden.

Let op 2: Voor het knijpen met een zogenaamde 'pinchgrip', hand-arm trillingen en langdurig kracht leveren met de handen zijn geen significante associaties vastgesteld met CTS. Veel werken met de computer resulteerde juist in een kleinere kans op CTS vergeleken met weinig computerwerk.

Strain Index Scoring Sheet

Date:		Task:	
Company:		Supervisor:	
Dept:		Evaluator:	

Risk Factor	Rating Criterion	Observation			Multiplier	Left	Right
Intensity of Exertion (Borg Scale - BS)	Light	Barely noticeable or relaxed effort (BS: 0-2)			1		
	Somewhat Hard	Noticeable or definite effort (BS: 3)			3		
	Hard	Obvious effort; Unchanged facial expression (BS: 4-5)			6		
	Very Hard	Substantial effort; Changes expression (BS: 6-7)			9		
	Near Maximal	Uses shoulder or trunk for force (BS: 8-10)			13		
Duration of Exertion (% of Cycle)	< 10%	**Calculated Duration of Exertion** (from inputs below)			0.5		
	10-29%	**User Inputs**	**Left**	**Right**	1.0		
	30-49%	Total observation time (sec.)			1.5		
	50-79%	Single exertion time (sec.)			2.0		
	≥ 80%	Number of exertions during observation time			3.0		
	Calculated Duration of Exertion (%)						
Efforts Per Minute	< 4	**Calculated Efforts Per Minute** (from inputs above)			0.5		
	4 - 8		**Left**	**Right**	1.0		
	9 - 14				1.5		
	15 - 19				2.0		
	≥ 20				3.0		
Hand/Wrist Posture	Very Good	Perfectly Neutral			1.0		
	Good	Near Neutral			1.0		
	Fair	Non-Neutral			1.5		
	Bad	Marked Deviation			2.0		
	Very Bad	Near Extreme			3.0		
Speed of Work	Very Slow	Extremely relaxed pace			1.0		
	Slow	Taking one's own time			1.0		
	Fair	Normal speed of motion			1.0		
	Fast	Rushed, but able to keep up			1.5		
	Very Fast	Rushed and barely/unable to keep up			2.0		
Duration of Task Per Day (hours)	<1				0.25		
	1 < 2				0.50		
	2 < 4				0.75		
	4 ≤ 8				1.00		
	> 8				1.50		

Figuur 1. Engelstalig voorbeeld van het scoreformulier van de Strain Index (Moore en Garg, 1995), https://www.tandfonline.com/doi/abs/10.1080/15428119591016863 en een link naar een Nederlands score formulier **<link>**

Stap 4. Nagaan van andere mogelijke oorzaken en de rol van de individuele gevoeligheid

CTS komt vooral bij (https://www.thuisarts.nl/carpale-tunnelsyndroom/ik-heb-carpale-tunnelsyndroom, UpToDate Carpal tunnel syndrome: Pathophysiology and risk factors):
45 tot 64 jarigen
vrouwen; vaak tijdens zwangerschap en borstvoeding, of in de menopauze
reumatoïde artritis
artrose van de hand (aan de duimzijde)
te langzaam of te snel werkende schildklier
diabetes

overgewicht
na een breuk in de hand of pols

Stap 5. Concluderen en melden

CTS kan als beroepsziekte worden gemeld als de bedrijfsarts van mening is dat na het doorlopen van bovenstaande stappen één of meer van de vier genoemde werkgerelateerde risicofactoren in overwegende mate de oorzaak is.

Stap 6. Preventieve maatregelen en interventies inzetten en evalueren

Werk dient bij voorkeur te worden uitgevoerd met:
Een Strain Index < 6,1
Mate van handkracht < 4 op de Borg-10 schaal (maximaal 'redelijk')
Een blootstelling lager dan de Hand Activity Level score van de ACGIH
Repeterend werk met een Hand Activity Level score < 5.
Specifieke studies naar het effect van preventieve maatregelen in werk op het verkleinen van het risico op CTS zijn niet gevonden. De oplossing dient dus te worden gekozen op basis van werkplekonderzoek en in samenspel tussen werkgever, werknemer, bedrijfsarts, en preventisten zoals arbeidshygiënisten, ergonomen of bedrijfsfysiotherapeuten. Voorbeelden van oplossingen uit de praktijk zijn mogelijk beschreven in de arbocatalogi voor diverse sectoren en branches: https://www.arboportaal.nl/externe-bronnen/arbocatalogi. Ook de volgende website kan van nut zijn:
https://www.arboportaal.nl/onderwerpen/werkhoudingen

Literatuur

Federatie Medisch Specialisten. Carpaletunnelsyndroom, https://richtlijnendatabase.nl/richtlijn/carpaletunnelsyndroom_cts/startpagina_-_carpaletunnelsyndroom_cts.html

Hassan, A, Beumer, A, Kuijer, PPFM, van der Molen, HF. Work-relatedness of carpal tunnel syndrome: systematic review including meta-analysis and GRADE. Health Sci Rep. 2022; 5:e888. https://onlinelibrary.wiley.com/doi/full/10.1002/hsr2.888

Moore J. Steven & Arun Garg (1995) The Strain Index: A Proposed Method to Analyze Jobs For Risk of Distal Upper Extremity Disorders, American Industrial Hygiene Association Journal, 56:5, 443-458, DOI: 10.1080/15428119591016863

NVAB richtlijn 2014, Handelen van de bedrijfsarts bij werknemers met klachten aan arm, nek of schouder (KANS) (gedeeltelijk herziene versie) https://nvab-online.nl/sites/default/files/bestanden-webpaginas/02-04-2015%20Herziene%20RL%20KANS_0.pdf, geraadpleegd 9 august 2021

Van der Molen Henk, Paul Kuijer, Gerda de Groene, Bas Sorgdrager, Jaap Maas, Teus Brand, Herman Bartstra, Willem Pieter Piebenga, Sietske Tamminga, Marijke Schutte. Kerncijfers Beroepsziekten in cijfers 2022, ISBN 978 94 91043 23 9, https://www.beroepsziekten.nl/content/covid-19-de-meest-gemelde-beroepsziekte-2021

Van der Molen HF, Visser S, Alfonso JH, Curti S, Mattioli S, Rempel D, Roquelaure Y, Kuijer PPFM, Tamminga SJ. Diagnostic criteria for musculoskeletal disorders for use in occupational healthcare or research: a scoping review of consensus- and synthesised-based case definitions. BMC Musculoskelet Disord. 2021b Feb 11;22(1):169. doi: 10.1186/s12891-021-04031-z. PMID: 33573616; PMCID: PMC7879660.

Verbeek J. When Work is Related to Disease, What Establishes Evidence for a Causal Relation? Saf Health Work. 2012 Jun;3(2):110-6. doi: 10.5491/SHAW.2012.3.2.110. Epub 2012 Jun 8. PMID: 22993715; PMCID: PMC3440459.

Bijlage I Work-relatedness of carpal tunnel syndrome: systematic review including meta-analysis and GRADE https://onlinelibrary.wiley.com/doi/full/10.1002/hsr2.888

Abstract

Background and aims: Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome with a high prevalence among workers. Insights on the physical work-related risk factors is necessary to develop appropriate preventative methods. The objective of this systematic review, including meta-analyses, is to assess which physical work-related risk factors are associated with carpal tunnel syndrome.

Methods: Systematic literature searches were carried out using PubMed and Embase until September 6, 2021. Studies were included if: 1) CTS was clinically assessed, 2) the studies were prospective cohort studies and 3) the exposure was reported using terms of exposed/less or non-exposed. Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: In total, 9270 patients with CTS from a population of 1,051,707 workers were included from seventeen studies. Meta-analyses revealed high-quality evidence for associations between CTS and high exposures to repetition (HR 1.87, 95%CI 1.42-2.46), force intensity (HR 1.84, 95%CI 1.22-2.79), exposures above hand activity level of ACGIH (HR 1.75, 95%CI 1.40-2.17) and the Strain Index >10 (HR 1.58, 95%CI 1.09-2.30). No significant associations were found for pinch gripping, hand-arm vibration or force duration. High computer-use exposure was significantly associated with a decreased rate of work-related CTS (HR 0.28, 95% CI 0.12-0.64).

Conclusion: This systematic review of prospective cohort studies found high certainty for an increased rate of CTS due to a high Strain Index, exposures exceeding the Activity Level of ACGIH, and high force intensity and high repetition. Workers performing tasks requiring both high force and high repetition even have a higher rate of developing CTS.

Introduction

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome and is caused by pressure on or around the median nerve. The carpal tunnel is a narrow passageway located at the palm side of the hand and is defined by the carpal ligament at the volar side where some tendons of the fingers (flexor digitorum profundus, flexor digitorum superficialis and flexor pollicis longus) and the median nerve run through. Compression of the median nerve causes tingling,

weakness and numbness in the thumb, index finger, middle finger and on the radial side of the ring finger.[1,2]
In de past two decades several studies have been performed to identify personal and psychosocial risk factors for CTS, but not often with a prospective study design to assess causal associations between risk factors and CTS. Examples of reported personal risk factors are sex, age, pregnancy, obesity, square wrists and comorbid diseases such as, rheumatoid arthritis, diabetes and thyroid diseases.[3-5] Studies have also shown that CTS might affect postmenopausal women and women taking oral contraception.[6,7] More recently, studies have described an association between psychosocial factors and carpal tunnel syndrome such as job strain and dissatisfaction.[8,9]
Although personal and psychosocial factors have been associated with CTS, CTS is still seen as a frequently occurring occupational disease probably caused by work/related.[10] Luckhaupt et al concluded that the overall lifetime prevalence of clinician-diagnosed CTS among current workers was 6.7% and the 12-month prevalence was 3.1%, representing approximately 4.8 million workers with current CTS.[11] This high prevalence also leads to high sickness absence rates after carpal tunnel release and the average return to work ranges from 21 days for non-manual to 39 days for manual work.[12] We do know that the problem is not only a financial issue, as some workers can't fulfill their jobs anymore and may need to find another job, also employers may suffer indirect costs such as loss of productivity and time spent on hiring new employees[13]
Since CTS is associated with many risk factors, it is important to look into the work-related population attributive fraction (PAF) of CTS. This indicates the proportion of incidents of CTS in the population that are attributable to work. Roquelaure et al.[14], a study regarding the attributable risk of CTS in the general population, showed a PAF of 50% for males performing manual work and 19% for females. This suggests that the incidence of CTS caused by work might decrease by introducing changes in the workplace. Given the association with manual work, it is important to determine the work-related physical risk factors of CTS to lower the incidence. Therefore, we decided to include only work-related physical risk factors in this review. Moreover, we presume that physical risk factors are likely to be explained by the pathophysiologic mechanisms in CTS.[15,16] Therefore, these physical risk factors are more likely to be causative for CTS and coherent preventive measures probably more effective to reduce the risk of manual work.
The American Academy of Orthopaedic Surgeon (AAOS) published a guideline in 2016 for the management of CTS, in which they described risk factors of CTS sorted into limited, moderate and strong evidence. They found an increased risk of CTS due to repetition with strong evidence. Moderate evidence was found for the following risk factors are: vibration, computer use and force.[17]
Complementary to that, a number of reviews have been published over the past two decades, for example van Rijn et al[18], Barcenilla et al.[19] and Kozak et al[20]. These reviews assessed cross-sectional, case-control and cohort studies to determine the occupational risk factors concluded that repetition, force, vibration and wrist bending are risk factors for carpal tunnel syndrome. In order to properly infer causality between work-related risk factors and CTS, it is preferred to use longitudinal studies preferably also adjusting for confounding factors.
Hence, we conducted a systematic review, including meta-analyses with evidence synthesis using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, using only prospective cohort studies to determine the association between physical work-related risk factors and clinically assessed CTS. The aim of this systematic review is to investigate which work-related physical risk factors are associated with clinically diagnosed CTS.

Methods

This systematic review, including a meta-analysis, was conducted according to the criteria of the PRISMA statement.[21]

Eligibility criteria

Only cohort-studies published in peer reviewed journals fulfilling the following criteria were used: the study was written in English, German, French, Italian or Dutch; CTS was clinically assessed; the association between CTS and the work-related physical risk factors was described using the effect measures, hazard ratio (HR), relative risk (RR) or could be calculated with the provided data; exposure data were provided for CTS and at least two levels of exposures were reported to retrieve a risk estimate. The clinical examination should report at least symptoms and signs as tingling, weakness and numbness in the thumb, index finger, middle finger and on the radial side of the ring finger. Physical work-related risk factors had to be described in terms of physical workload or specific occupational activities such as repetitive hand movements or postures. No studies were excluded on the basis of the year of publication.

Literature search

Systematic literature searches were carried out using PubMed and Embase from 1954 to December 2[nd] 2021. We combined several CTS terminologies and work-related physical risk factors to generate the search strategy. The search strategies used in both databases are shown in appendix 1.

Study selection

After duplicates from PubMed and Embase had been removed, all studies were checked independently and blinded for each other by at least two of the authors. Firstly, titles and abstracts were screened to identify relevant studies and to exclude studies that did not fulfil the inclusion criteria. Secondly, we obtained the full texts of the remaining studies and assessed those for eligibility. Disagreement was resolved by discussion between the two authors, and if needed a third author was asked. Endnote X9 and Rayyan were used to manage the screening and selection.

Data extraction

The following data were extracted from each article: author; year of publication; country; study design; case definition of CTS; length of follow-up; definition of work-related physical risk factors; method of assessment of work-related risk factors; number and characteristics of participants such as sex and age; risk estimate and confidence interval; and adjustment for confounding.

Quality assessment

The methodological quality of the study was rated independently by two authors. Since we only included prospective cohort studies, we used the Quality in Prognosis Studies (QUIPS) tool. The checklist covers six domains: 1) study population (e.g. the study sample represents the population of interest), 2) study attrition (e.g. the response rate was >80%), 3) prognostic factor measurement (e.g. the exposure was assessed by professionals), 4) outcome measurement (e.g. CTS was clinically assessed), 5) study confounding (e.g. the risk-estimate was adjusted for age, sex, BMI and diabetes mellitus), 6) statistical analysis and reporting (e.g. a risk-estimate was calculated). Every domain was scored as having a low, moderate or high risk of bias.[22] The overall quality of the studies was classified as having a high risk of bias if one domain was scored as having a high risk of bias or two domains were scored as having a moderate risk of bias.

Data analysis

A meta-analysis was performed if there were at least two studies to determine whether work-related physical risk factors were associated with CTS. For each risk factor, we used the highest vs. the lowest exposures as reported in the studies. If the exposure was trichotomized, we used the reported medium exposed group as exposed category and the reported low exposure as reference category. A pooled hazard ratio (HR) and 95% confidence interval (CI) were calculated for each risk factor using a random effects model in Cochrane's RevMan 5.4. Heterogeneity was assessed using the I^2 test, which describes the dispersion of effect sizes and the relative heterogeneity in the studies as compared to random chance. Heterogeneity was considered high if $I^2 > 70\%$. Forest plots were made for each risk factor to visualise the pooled results.

GRADE

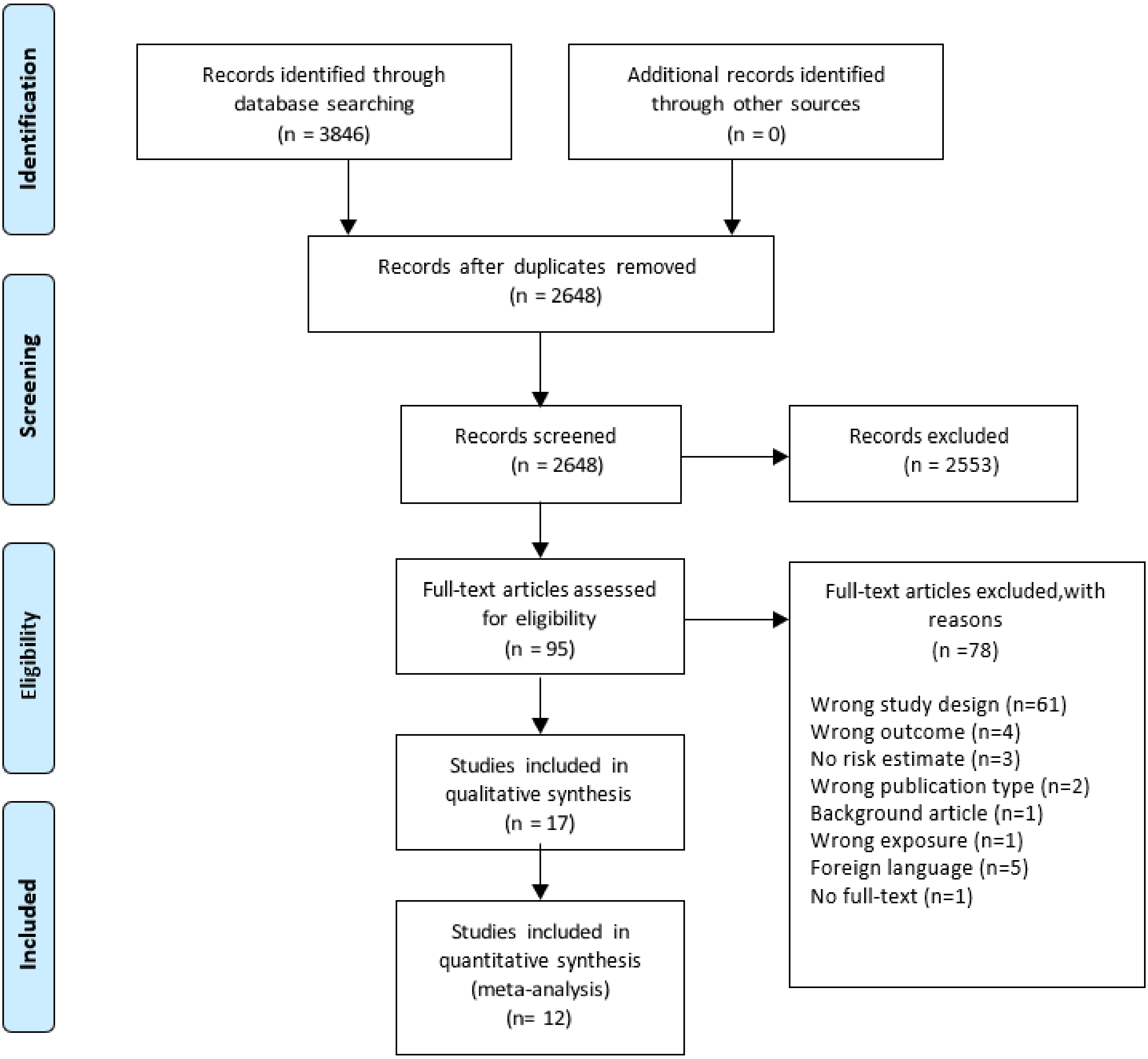
To assess the certainty of evidence for the association between physical work-related risk factors and CTS of risk factors that were included in the meta-analyses we used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.[23] GRADE uses four levels to judge the certainty of evidence: very low, low, moderate and high. Since we included only prospective cohort studies that studied an association between specific risk factors and CTS, the starting qualification of certainty of evidence for each risk factor was high. The quality of evidence was downgraded on the basis of the following five factors: 1) study limitation (high risk of bias present in the majority of the studies), 2) inconsistency ($I^2 > 70\%$), 3) indirectness (CTS not clinically assessed), 4) imprecision (range of the 95% Confidence Interval >2.0), and 5) presence of publication bias. If the quality of evidence was not downgraded on the basis of these five criteria, it could be upgraded on the basis of two factors: 1) large effect size (the risk estimate of a risk factor >2.5), and 2) presence of a dose-effect relationship in the reported study. Two authors independently assessed the quality criteria and the level of agreement was discussed in the whole author group.

Results

Study selection

Our search strategy resulted in 3846 studies of which 1202 were duplicates. After our first screening of the titles and abstracts we excluded 2551 articles that did not meet our inclusion criteria’s. The remaining 97 articles were assessed in our full-text screening. In total, 17 studies[24-40] were included and 12 of these studies were enrolled in our meta-analysis. Three studies[26,28,29] used the same pooled cohorts with the same participants and because of that we chose the study[27] with the most participants in the meta-analysis. The study selection process is shown in a PRISMA flowchart in figure 1.

Figure 1: Flow chart of the included studies



Study characteristics

All the studies are prospective cohort studies and were published between 2001 and 2021. The included studies were conducted worldwide with eight studies in the United States[25-29,31,32,36], two in France[33,38], three in Italy[24,39,40], two in Finland[30,37], one in Denmark[34] and one in both the United States and France[35]. The total number of included workers was 1,051,707 and were all 18 years of age or older. In total, 9270 cases of CTS were clinically assessed but two studies did not mention the cases of CTS in their articles. CTS was clinically assessed in all the studies by symptoms with or without nerve conduction studies (NCS). Symptoms were tingling, numbness, pain and/or burning in two or more of the first four digits. Leclerc et al.[33], Lund et al.[34] and Roquelaure et al.[38] assessed CTS if these symptoms were present. Hulkkonen et al.[30] and Pourmemarie et al.[37] obtained data on hospitalizations due to CTS. The remaining studies assessed CTS by both the presence of the above-mentioned symptoms and NCS. Six studies studied the association between the ACGIH Threshold Limit Values (TLV) and the incidence of CTS[24,25,27,32,39,40]; four studies assessed the association between repetition and the incidence of CTS[26,28,29,40]; Four studies studied the association between force duration and the incidence of CTS[25,26,28,29]; Four studies assessed the association between vibration and the incidence of CTS[28,30,36,37]; six studies assessed the association between force intensity and the incidence of CTS[26,28,29,33,34,40]; two studies assessed the association between wrist bending posture and the incidence of CTS[28,38]; three studies assessed the association between pinch gripping and the incidence of CTS[33,37,38]; two studies assessed the association between computer/keyboard use and the incidence of CTS[35,36] and finally, two studies studied the association between a high Strain Index (SI) and the incidence of CTS.[27,31] The characteristics of the studies are described in appendix 2.

Quality of the studies
Bonfiglioli et al.[24] and Violante et al.[39] had the best quality and had a low risk of bias on all six domains. Seven studies[26,30,33,34-38,40] had a moderate risk of bias on the first domain because they did not provide a table with the baseline characteristics or did not have a sufficient number of participants in their study (<500 participants). All of our included studies, except two studies[24,40], did not provide a table with the baseline characteristics of the participants lost to follow up and on top of those five studies also had a low response rate (<70%). Studies[30,33,35,38] that measured the exposure by a self-administered questionnaire had a high risk of bias on the third domain and one study[37] that measured the exposure by interviews had a moderate risk of bias on the third domain. Lastly, five studies[25,26,33,36,38] did not measure all the confounders and had a moderate/high risk of bias on the fifth domain. The complete assessment of the studies is shown in table 1.
Risk factors and CTS

Table I: Assessment of the risk of bias using the Quality in Prognostic Studies (QUIPS) tool

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Bonfiglioli[24] 2013						
Burt[25] 2013						
Dale[26] 2015						
Garg[27] 2012						
Harris-Adamson[28] 2015						
Harris-Adamson[29] 2016						
Hulkkonen[30] 2020						
Kapellusch[31] 2021						
Kapellusch[32] 2014						
Leclerc[33] 2001						
Lund[34] 2019						
Mediouni[35] 2015						
Nathan[36] 2005						
Pourmemari[37] 2018						
Roquelaure[38] 2020						
Violante[39] 2007						
Violante[40] 2016						

Green indicates a low risk
Yellow indicates a moderate risk
Red indicates a high risk

Meta-analysis and GRADE

We performed a meta-analysis for the following risk factors: repetition, force duration, force intensity, ACGIH Threshold Limit Values (TLV), vibration, pinch gripping computer use, the Strain Index (SI). We could not perform a meta-analysis for the following risk factor: wrist bending posture because there were not enough studies to include in the meta-analysis. Details of the assessment of the GRADE framework are presented in table 2.

Table II: Grading of Recommendations Assessment Development and Evaluations (GRADE) framework for the work-related physical risk factors for carpal tunnel syndrome

Work-related physical risk factor	Number of participants (number of Incident cases of CTS)	Prospective cohort studies	Phase of investigation, 1=explorative: ↓ 2/3=explanatory	Study limitations, majority of studies high risk of bias: ↓	Inconsistency, (i^2 >50%)↓	Indirectness Diagnosis (not clinically assessed)↓	Imprecision CI effect size: (<1 and >2), (Range >2) Yes: ↓	Publication bias strongly suspected, Yes: ↓	Effect size HR>2.5↑	Dose–response present:↑	Overall quality (high, moderate, low, very low)
ACGIH TLV[27,32,39,40]	6767 (324)	4/4	2	Low 0/4	0%	0/4	1.40-2.17	Not detected	1.75	No	High
Repetition[28,40]	6345 (211)	2/2	2	Low 0/2	31%	0/2	1.42-2.46	Not detected	1.87	No	High
Forceful duration[25,28]	3542 (133)	2/2	2	Low 1/2↓	45%	0/2	0.98-3.31↓	Not detected	1.80	No	Low
Vibration[28,30,37]	17,717 (467)	3/3	2	High 2/3↓	90%↓	0/3	0.63-3.42↓	Not detected	1.47	No	Very low
Force intensity[28,33,40]	6503 (218)	3/3	2	Low 1/3	0%	0/3	1.22-2.79	Not detected	1.84	No	High
Pinch gripping[33,37,38]	7702 (150)	3/3	2	High 3/3↓	55%↓	0/3	0.96-3.52↓	Not detected	1.84	No	Very low
Computer use[36]	2262 (56)	2/2	2	High 1/2 ↓	30%	0/2	0.12-0.64	Not detected	0.28	No	Moderate
Strain Index[27,31]	1801 (192)	2/2	2	0/2	17%	0/2	1.09-2.30	Not detected	1.58	No	High

↓ indicates a down-grade

Repetition and CTS

Repetition was measured using the HAL-scale, which is a 10-point scale that rates the repetitiveness of hand use and also accounts for pauses and efforts.[41] The meta-analysis showed, based on two studies[28,40], that there was high-quality evidence that high exposure of repetition is significantly associated with an increased rate of the onset of CTS (HR 1.87, 95%CI 1.42-2.46) (Figure 2c).

Force and CTS

Force was measured using two methods. We made a distinction between force intensity, which measures the actual perceived force, and force duration, which measures the duration of time in forceful exertion. This resulted in two forest plots regarding force and CTS.
Force intensity was measured using the Borg-10 scale, which estimates an individual's effort, exertion and breathlessness during physical tasks.[42] The meta-analysis showed, based on three studies[28,33,40], that there was high-quality evidence that high exposure of force is significantly associated with an increased rate of the onset of CTS (HR 1.84, 95%CI 1.22-2.79) (Figure 2d).
Force duration was measured in percentage of time in forceful exertion. The meta-analysis showed, based on two studies[25,28], that there was very low-quality evidence that high exposure of forceful exertion is not significantly associated with an increased rate of the onset of CTS (HR 1.80, 95%CI 0.98-3.31) (Figure 2e).

ACGIH Threshold Limit Values (TLV) and CTS

The ACGIH Threshold Limit Values (TLV) is a method to assess the risk on the overload of the wrists and hands of workers. It combines two parameters: the Hand Activity Level (HAL) and normalized Peak Force (nPF). ACGIH differentiates between three levels of exposure. Below Activity Level (AL) is the lowest level, AL to Threshold Limit Value (TLV) is the intermediate level and above TLV is the highest level.[43] In our meta-analyse we used <AL as the low exposure and ≥AL + <TLV (intermediate) as the high exposure. The meta-analysis showed, based on four studies[27,32,39,40], that there was high-quality evidence that the high exposure is significantly associated with an increased rate of the onset of CTS (HR 1.75, 95%CI 1.40-2.17) (Figure 2a).

Vibration and CTS

Low exposure was defined as not/lightly using a vibration tool and high exposure was defined as using a vibration tool. The meta-analysis showed, based on three studies[28,30,37], that there was very low-quality evidence that high exposure of vibration is not significantly associated with an increased rate of the onset of CTS (HR 1.47, 95%CI 0.63-3.42) (Figure 2b).

Pinch gripping and CTS

High exposure was defined as gripping for more than 4 hours a day or any pinch grip force. The meta-analysis showed, based on three studies[33,37,38], that there was very low-quality evidence that high exposure of pinch gripping is not significantly associated with an increased rate of the onset of CTS (HR 1.84, 95%CI 0.96-3.52) (Figure 2f).

Computer/keyboard use and CTS

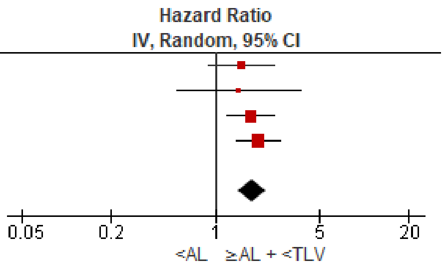
Low exposure was defined as never or almost never using a computer and high exposure was defined as using a computer all or almost all day. The meta-analysis showed, based on one study with two cohorts[35], that there was moderate-quality evidence that high exposure of computer use is significantly associated with a decreased rate of the onset of CTS (HR 0.28, 95%CI 0.12-0.64) (Figure 2g).

Figure 2: Forest plots of the eight work-related physical risk factors for developing carpal tunnel syndrome

(a)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Violante 2007	0.4055	0.2606	18.3%	1.50 [0.90, 2.50]	2007
Garg 2012	0.3633	0.4904	5.2%	1.44 [0.55, 3.76]	2012
Kapellusch 2014	0.5451	0.1894	34.6%	1.72 [1.19, 2.50]	2014
Violante 2016	0.6595	0.1722	41.9%	1.93 [1.38, 2.71]	2016
Total (95% CI)			**100.0%**	**1.75 [1.40, 2.17]**	

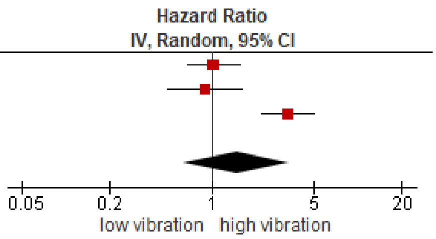
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 5.01 (P < 0.00001)



(b)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Harris-Adamson 2015	0.0336	0.2065	34.3%	1.03 [0.69, 1.55]	2015
pourmemarie 2018	-0.1054	0.2999	31.5%	0.90 [0.50, 1.62]	2018
hulkkonen 2020	1.1997	0.2121	34.2%	3.32 [2.19, 5.03]	2020
Total (95% CI)			**100.0%**	**1.47 [0.63, 3.42]**	

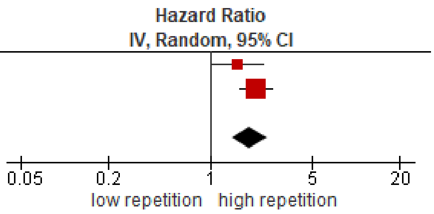
Heterogeneity: Tau² = 0.50; Chi² = 19.98, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 0.90 (P = 0.37)



(c)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Harris-Adamson 2015	0.4307	0.2096	34.0%	1.54 [1.02, 2.32]	2015
Violante 2016	0.7254	0.1271	66.0%	2.07 [1.61, 2.65]	2016
Total (95% CI)			**100.0%**	**1.87 [1.42, 2.46]**	

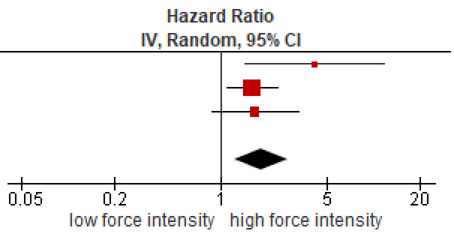
Heterogeneity: Tau² = 0.01; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 4.48 (P < 0.00001)



(d)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Leclerc 2001	1.4086	0.5362	13.6%	4.09 [1.43, 11.70]	2001
Harris-Adamson 2015	0.4682	0.1949	57.1%	1.60 [1.09, 2.34]	2015
Violante 2016	0.5166	0.3346	29.3%	1.68 [0.87, 3.23]	2016
Total (95% CI)			**100.0%**	**1.84 [1.22, 2.79]**	

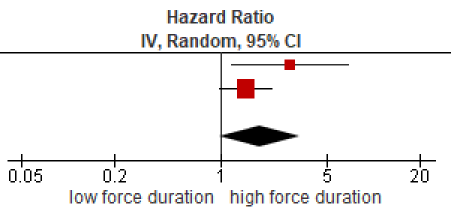
Heterogeneity: Tau² = 0.04; Chi² = 2.74, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 2.89 (P = 0.004)



(e)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Burt 2013	1.0405	0.4464	32.0%	2.83 [1.18, 6.79]	2013
Harris-Adamson 2015	0.3773	0.2028	68.0%	1.46 [0.98, 2.17]	2015
Total (95% CI)			**100.0%**	**1.80 [0.98, 3.31]**	

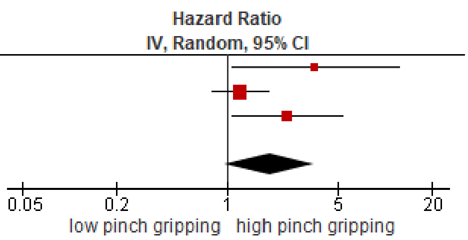
Heterogeneity: Tau² = 0.10; Chi² = 1.83, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 1.91 (P = 0.06)



(f)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Leclerc 2001	1.2757	0.6212	19.3%	3.58 [1.06, 12.10]	2001
pourmemarie 2018	0.1823	0.2069	49.2%	1.20 [0.80, 1.80]	2018
Roquelaure 2020	0.8714	0.4101	31.5%	2.39 [1.07, 5.34]	2020
Total (95% CI)			**100.0%**	**1.84 [0.96, 3.52]**	

Heterogeneity: Tau² = 0.18; Chi² = 4.42, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.85 (P = 0.06)



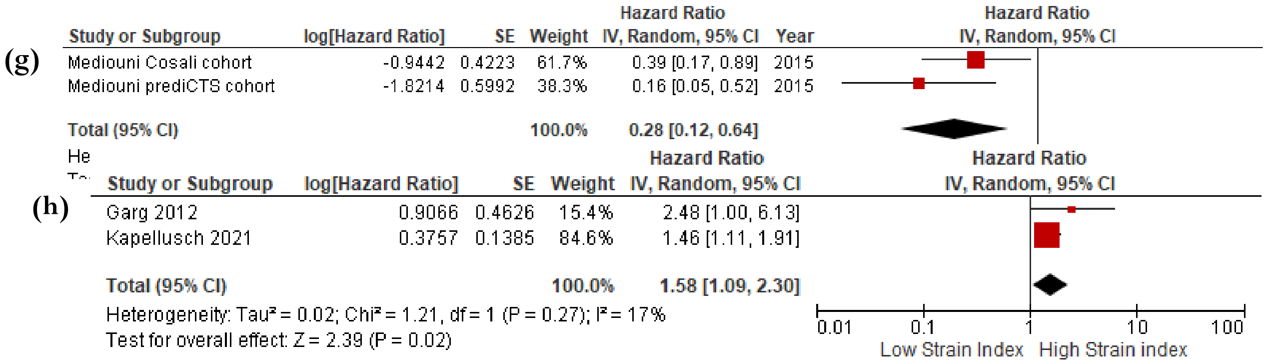


Figure Legend: (a) Forest plot of comparison < Action Limit vs. ≥Action limit + < Threshold Limit Value. (b) Forest plot of comparison low vibration vs. high vibration. (c) Forest plot of comparison low repetition vs. high repetition. (d) Forest plot of comparison low force intensity vs. high force intensity. (e) Forest plot of comparison low force duration vs. high force duration. (f) Forest plot of comparison low pinch gripping vs. high pinch gripping. (g) Forest plot of comparison high computer use vs. low computer use. (h) Forest plot of comparison low Strain Index vs. high Strain Index

The Strain Index (SI) and CTS

The SI is an index that assesses the physical exposure of the distal upper extremities based on frequency, duration, intensity and hand/wrist posture.[44] Kappellusch et al.[31] defined the high exposure as SI>10 and Garg et al.[27] defined the high exposure as SI>6.1 This meta-analysis showed that there was high-quality evidence that high exposure of the SI is significantly associated with an increased rate of the onset of CTS (HR 1.58, 95% CI 1.09-2.30) (Figure 2h).

Wrist bending posture and CTS

Roquelaure et al. measured the wrist bending posture as time spent in wrist bending. They differentiated three levels of exposure: low (0 hours a day), moderate (2 to 4 hours a day) and high (more than 4 hours a day).[38] The moderate exposure had a HR of 1.61 with 95% CI of 0.79-3.29 and the high exposure had a HR of 1.63 with 95% CI of 0.70-3.78 (Table 1). Harris-Adamson et al.[28] measured the wrist bending posture as percentage of time spent in ≥30°wrist flexion or extension. The high exposure of flexion (>1%) had a HR of 0.87 with 95% CI of 0.59-1.29 and the high exposure of extension (>5%) had a HR of 0.83 with 95% CI of 0.60-1.15 (appendix 2).

Discussion

Main findings

This systematic review with meta-analyses showed high certainty for a significantly increased rate of CTS due to force duration (71%), force intensity (47%) and repetition (64%). Workers that perform tasks requiring both force and repetition even have an 80% higher rate of developing CTS, as seen in the meta-analysis for the ACGIH Threshold Limit Values, again with high certainty. We found a significantly increased rate of CTS due to the Strain Index (45%). No associations for hand-arm vibration and pinch-gripping with CTS were found, with low-quality certainty. No associations were also found for wrist bending due to contradictory outcomes of the two included studies. Computer

use was found to reduce the risk of work-related CTS with 72% with moderate-quality certainty. However, in the current study low exposure was defined as never or almost never using a computer and high exposure as using a computer all or almost all day. Therefore, the reference group might be a high risk CTS group performing work characterised by high exposure to force and repetition. Future studies on CTS and computer use are needed that compare high versus low exposure to computer use in terms of posture, repetition and force, for instance comparing all day data entry jobs with other types of office work having more variability and thereby less exposure to computer use.
Although Barcenilla et al.[19], reporting about a meta-analysis on CTS and occupation, did find a significant association for vibration, our meta-analysis did not show sufficient evidence for this association. A possible explanation is that we included studies with a lower risk of bias in our meta-analysis. In general, our conclusion is in line with the study of Kozak et al.[20] , which is an overview of systematic reviews. In their meta-analysis they also concluded that in current high-quality primary studies vibration is not an independent risk factor of CTS. In line with our results, Barcenilla et al.[19] also found a significant association between force and repetition and the incidence of CTS. For both risk factors, they reported higher risks estimates than we found: for force OR=4.23 (95%CI 1.53-11.68) versus our HR=1.84 (95%CI 1.22-2.79) and for repetition OR=2.26 (95%CI 1.73-2.94) versus our HR=1.87 (95%CI 1.42-2.46). This could also be due to the fact that we only used prospective cohort studies, while Barcenilla et al.[19] also included cross-sectional studies. Furthermore, our meta-analysis showed a significant association between the ACGIH Threshold Limit Values and CTS. This finding confirmed and strengthened the evidence as reported in the study of Kozak et al.[20]. The RR they reported was 1.54 (95%CI 1.02-2.31), which is lower than our HR of 1.75 (95%CI 1.40-2.17).
Two previous studies[45,46] reviewed the association between computer use and CTS. While those two studies did not find an association between computer use and CTS, our meta-analysis showed a reduced risk of CTS and computer use at work, possibly due to the fact that low-level hand-activity is a protective factor.
Lastly, our systematic review assessed whether pinch gripping and the Strain Index are risk factors for CTS. We did find a significant association between the Strain Index and an increased rate of CTS, and did not for pinch gripping

Methodological considerations

The strength of this review is that we only included prospective cohort studies, as these designs are the preferred evidence for inferring causality. In addition, we performed a meta-analysis and used GRADE for the assessment of the certainty of evidence. Our systematic review solely included prospective cohort studies and used GRADE to determine the certainty of evidence and therefore has high accuracy and precision.
Another strength is that CTS had to be clinically assessed. All the studies used the same set of symptoms (tingling, weakness and numbness in the thumb, index finger, middle finger and on the radial side of the ring finger) to diagnose CTS. Some studies did also require NCS in the diagnosis of CTS. We did not find a difference in risk estimates for studies using NCS versus those that did not. A proper clinical assessment is important to secure an accurate risk estimation because self-assessment of CTS could lead to an overestimation of the hazard ratios and the risk factors involved.
A limitation of our review is that five studies did not perform a (blinded) observation to assess exposure. Instead, they conducted an interview or collected information on exposure using a questionnaire. This is an important source of recall bias and possibly overestimation of exposure.

Awareness and prevention

Despite the available evidence of high certainty about work-related physical risk factors for CTS, there still might be a lack of awareness in clinical care for prevention. The study of Yagev et al.[47] on the recognition of occupational risk factors by clinicians showed that in 60% of the cases the clinician did not ask about the patient's job, and even when the job was mentioned, no further assessment was made regarding the specific tasks and activities in the job. In addition, fewer than 10% of the patients were referred to an occupational physician for further evaluation. The awareness of all clinicians is required for optimal patient care and to help the patient to promote preventative measures at work. Also in teaching, attention should be given to the importance of work as a possible aetiological risk factor for the development of CTS and enhance communication among various medical disciplines and active referral of patients who are at risk at work.[47]

Conclusion

This systematic review of prospective cohort studies found high certainty for an increased rate of CTS due to a high Strain Index, exposures exceeding the Activity Level of the ACGIH, and high force intensity and high repetition. Workers performing tasks requiring both high force and high repetition even have a higher rate of developing CTS. Therefore, we recommend to develop and implement preventive measures, especially for these two risk factors and to evaluate which measures best reduce the incidence of CTS.

References

1. Kothari MJ, Carpal tunnel syndrome: Clinical manifestations and diagnosis. UptoDate, 2021 July 17. [Cited 2021 Oct 29]. Available from: https://www.uptodate.com/contents/carpal-tunnel-syndrome-clinical-manifestations-and-diagnosis/contributor-disclosure.
2. Faust K, Jennings CD, Carpal Tunnel Syndrome. OrthoInfo, 2016 July. [Cited 2021 Oct 29]. Available from: https://orthoinfo.aaos.org/en/diseases--conditions/carpal-tunnel-syndrome/.
3. Geoghegan JM, Clark DI, Bainbridge LC, Smith C, Hubbard R. Risk factors in carpal tunnel syndrome. J Hand Surg Br. 2004 Aug;29(4):315-20.
4. Ablove RH, Ablove TS. Prevalence of carpal tunnel syndrome in pregnant women. WMJ. 2009 Jul;108(4):194-6.
5. Vashishtha M, Varghese B, Mosley F, Kadakia A, de Jager W. Screening for thyroid dysfunction and diabetes in patients with carpal tunnel syndrome. Surgeon. 2016 Jun;14(3):147-9.
6. Ferry S, Hannaford P, Warskyj M, Lewis M, Croft P. Carpal tunnel syndrome: a nested case-control study of risk factors in women. Am J Epidemiol. 2000 Mar 15;151(6):566-74.
7. Kaplan Y, Kurt SG, Karaer H. Carpal tunnel syndrome in postmenopausal women. J Neurol Sci. 2008 Jul 15;270(1-2):77-81.
8. Mansfield M, Thacker M, Sandford F. Psychosocial Risk Factors and the Association With Carpal Tunnel Syndrome: A Systematic Review. Hand (N Y). 2018 Sep;13(5):501-508.
9. Roquelaure Y, Garlantézec R, Evanoff BA, Descatha A, Fassier JB, Bodin J. Personal, biomechanical, psychosocial, and organizational risk factors for carpal tunnel syndrome: a structural equation modeling approach. Pain. 2020 Apr;161(4):749-757.
10. Kao SY. Carpal Tunnel Syndrome As an Occupational Disease. The Journal of the American Board of Family Practice November 2003, 16 (6) 533-542;
11. Luckhaupt SE, Dahlhamer JM, Ward BW, Sweeney MH, Sestito JP, Calvert GM. Prevalence and work-relatedness of carpal tunnel syndrome in the working population, United States, 2010 National Health Interview Survey. Am J Ind Med. 2013 Jun;56(6):615-24.
12. Newington L, Stevens M, Warwick D, Adams J, Walker-Bone K. Sickness absence after carpal tunnel release: a systematic review of the literature. Scand J Work Environ Health. 2018 Nov 1;44(6):557-567.
13. Shahid S. The Economic Costs of Carpal Tunnel Syndrome in the Workplace. https://www.linkedin.com/pulse/economic-costs-carpal-tunnel-syndrome-workplace-shahriar-shahid. Accessed on December 09 2021.
14. Roquelaure Y, Ha C, Fouquet N, Descatha A, Leclerc A, Goldberg M, et al. Attributable risk of carpal tunnel syndrome in the general population: implications for intervention programs in the workplace. Scand J Work Environ Health. 2009 Oct;35(5):342-8.
15. Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol. 2002 Sep;113(9):1373-81.
16. Aboonq MS. Pathophysiology of carpal tunnel syndrome. Neurosciences (Riyadh). 2015 Jan;20(1):4-9
17. American Academy of Orthopaedic Surgeon Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline. https://www.aaos.org/globalassets/quality-and-practice-resources/carpal-tunnel/cts-cpg_4-25-19.pdf. Published February 29, 2016. Accessed on April 8 2022
18. van Rijn RM, Huisstede BM, Koes BW, Burdorf A. Associations between work-related factors and the carpal tunnel syndrome--a systematic review. Scand J Work Environ Health. 2009 Jan;35(1):19-36.

19. Barcenilla, A., March, LM,; Chen, JS, Sambrook, PN. Carpal tunnel syndrome and it`s relationship to occupation: a meta-analysis. Rheumatology, 51(2), 250–261.
20. Kozak A, Schedlbauer G, Wirth T, Euler U, Westermann C, Nienhaus A. Association between work-related biomechanical risk factors and the occurrence of carpal tunnel syndrome: an overview of systematic reviews and a meta-analysis of current research. BMC Musculoskelet Disord. 2015 Sep 1;16:231.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009;339:b2535.
22. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013 Feb 19;158(4):280-6.
23. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71.
24. Bonfiglioli R, Mattioli S, Armstrong TJ, Graziosi F, Marinelli F, Farioli A, Violante FS. Validation of the ACGIH TLV for hand activity level in the OCTOPUS cohort: a two-year longitudinal study of carpal tunnel syndrome. Scand J Work Environ Health. 2013 Mar 1;39(2):155-63.
25. Burt S, Deddens JA, Crombie K, Jin Y, Wurzelbacher S, Ramsey J. A prospective study of carpal tunnel syndrome: workplace and individual risk factors. Occup Environ Med. 2013 Aug;70(8):568-74.
26. Dale AM, Ekenga CC, Buckner-Petty S, Merlino L, Thiese MS, Bao S, et al. Incident CTS in a large pooled cohort study: associations obtained by a Job Exposure Matrix versus associations obtained from observed exposures. Occup Environ Med. 2018 Jul;75(7):501-506.
27. Garg A, Kapellusch J, Hegmann K, Wertsch J, Merryweather A, Deckow-Schaefer G, et al. The Strain Index (SI) and Threshold Limit Value (TLV) for Hand Activity Level (HAL): risk of carpal tunnel syndrome (CTS) in a prospective cohort. Ergonomics. 2012;55(4):396-414.
28. Harris-Adamson C, Eisen EA, Kapellusch J, Garg A, Hegmann KT, Thiese MS, et al. Biomechanical risk factors for carpal tunnel syndrome: a pooled study of 2474 workers. Occup Environ Med. 2015 Jan;72(1):33-41.
29. Harris-Adamson C, Eisen EA, Neophytou A, Kapellusch J, Garg A, Hegmann KT, et al. Biomechanical and psychosocial exposures are independent risk factors for carpal tunnel syndrome: assessment of confounding using causal diagrams. Occup Environ Med. 2016 Nov;73(11):727-734.
30. Hulkkonen S, Shiri R, Auvinen J, Miettunen J, Karppinen J, Ryhänen J. Risk factors of hospitalization for carpal tunnel syndrome among the general working population. Scand J Work Environ Health. 2020 Jan 1;46(1):43-49.
31. Kapellusch JM, Bao SS, Malloy EJ, Thiese MS, Merryweather AS, Hegmann KT. Validation of the Revised Strain Index for Predicting Risk of Incident Carpal Tunnel Syndrome in a Prospective Cohort. Ergonomics. 2021 Jun 30:1-10.
32. Kapellusch JM, Gerr FE, Malloy EJ, Garg A, Harris-Adamson C, Bao SS, et al. Exposure-response relationships for the ACGIH threshold limit value for hand-activity level: results from a pooled data study of carpal tunnel syndrome. Scand J Work Environ Health. 2014 Nov;40(6):610-620.
33. Leclerc A, Landre MF, Chastang JF, Niedhammer I, Roquelaure Y; Study Group on Repetitive Work. Upper-limb disorders in repetitive work. Scand J Work Environ Health. 2001 Aug;27(4):268-78.
34. Lund CB, Mikkelsen S, Thygesen LC, Hansson GÅ, Thomsen JF. Movements of the wrist and the risk of carpal tunnel syndrome: a nationwide cohort study using objective exposure measurements. Occup Environ Med. 2019 Aug;76(8):519-526.

35. Mediouni Z, Bodin J, Dale AM, Herquelot E, Carton M, Leclerc A, Fouquet N, Dumontier C, Roquelaure Y, Evanoff BA, Descatha A. Carpal tunnel syndrome and computer exposure at work in two large complementary cohorts. BMJ Open. 2015 Sep 9;5(9):e008156.
36. Nathan PA, Istvan JA, Meadows KD. A longitudinal study of predictors of research-defined carpal tunnel syndrome in industrial workers: findings at 17 years. J Hand Surg Br. 2005 Dec;30(6):593-8.
37. Pourmemari MH, Heliövaara M, Viikari-Juntura E, Shiri R. Carpal tunnel release: Lifetime prevalence, annual incidence, and risk factors. Muscle Nerve. 2018 Oct;58(4):497-502.
38. Roquelaure Y, Garlantézec R, Evanoff BA, Descatha A, Fassier JB, Bodin J. Personal, biomechanical, psychosocial, and organizational risk factors for carpal tunnel syndrome: a structural equation modeling approach. Pain. 2020 Apr;161(4):749-757.
39. Violante FS, Armstrong TJ, Fiorentini C, Graziosi F, Risi A, Venturi S, et al. Carpal tunnel syndrome and manual work: a longitudinal study. J Occup Environ Med. 2007 Nov;49(11):1189-96.
40. Violante FS, Farioli A, Graziosi F, Marinelli F, Curti S, Armstrong TJ, et al. Carpal tunnel syndrome and manual work: the OCTOPUS cohort, results of a ten-year longitudinal study. Scand J Work Environ Health. 2016 Jul 1;42(4):280-90.
41. Latko, WA., Armstrong, TJ., Foulke, JA., Herrin, GD., Rabourn, RA., Ulin, SS. (1997). Development and evaluation of an observational method for assessing repetition in hand tasks. American Industrial Hygiene Association Journal, 58(4), 278-285.
42. Physiopedia contributors. Borg Rating Of Perceived Exertion [Internet]. Physiopedia, 2020 Sep 27. [cited 2021 Oct 26]. Available from: https://www.physio-pedia.com/index.php?title=Borg_Rating_Of_Perceived_Exertion&oldid=251587.
43. Yung M, Dale AM, Kapellusch J, Bao S, Harris-Adamson C, Meyers AR, et al. Modeling the Effect of the 2018 Revised ACGIH® Hand Activity Threshold Limit Value® (TLV) at Reducing Risk for Carpal Tunnel Syndrome. J Occup Environ Hyg. 2019 Sep;16(9):628-633.
44. Garg A, Moore JS, Kapellusch JM. The Revised Strain Index: an improved upper extremity exposure assessment model. Ergonomics. 2017 Jul;60(7):912-922.
45. Mediouni Z, de Roquemaurel A, Dumontier C, Becour B, Garrabe H, Roquelaure Y, et al. Is carpal tunnel syndrome related to computer exposure at work? A review and meta-analysis. J Occup Environ Med. 2014;56:204–8.
46. Thomsen JF, Gerr F, Atroshi I. Carpal tunnel syndrome and the use of computer mouse and keyboard: a systematic review. BMC Musculoskelet Disord. 2008;9:134.
47. Yagev Y, Gringolds M, Karakis I, Carel RS. Carpal tunnel syndrome: under-recognition of occupational risk factors by clinicians. Ind Health. 2007 Dec;45(6):820-2

Appendix 1: Search strategy in Pubmed and Embase

Pubmed	(("occupational disease*"[MeSH Terms]) OR ("occupational disease*"[Title/Abstract]) OR ("risk factor*"[MeSH Terms]) OR ("risk factor*"[Title/Abstract]) OR ("work-related"[Title/Abstract]) OR ("worker*"[Title/Abstract]) OR ("physical load"[Title/Abstract]) OR ("occupational exposure*"[Title/Abstract]) OR ("occupational exposure*"[MeSH Terms])) AND (("carpal tunnel syndrome"[Title/Abstract]) OR ("Median neuropathy"[MeSH Terms]) OR ("carpal tunnel syndrome"[MeSH Terms]) OR ("Median neuropathy"[Title/Abstract]))
Embase	((occupational disease* or risk factor* or work-related or physical load or occupational risk factor* or occupational exposure*).af) AND ((carpal tunnel syndrome or median neuropathy).af.)

Appendix 2: Study characteristics of the included studies

Author (reference)	Study population	County		Female (%)	Follow-up	Outcome assessment	Exposure assessment	Risk factor High versus No or Low exposure	Incidence of CTS	Hazard Ratio (95%C
	ACGIH Threshold Limit Values (TLV)									
Kapellusch[32] 2014	Full-time male and female study participants aged ≥18 and employed by 54 predominantly manufacturing and service companies located in ten US states (N=2751)	United States		1400 (51%)	2001-2010	Clinically assessed with NCS	Blinded observation by walk-through	<AL ≥AL + <TLV ≥TLV	90/1522 40/512 50/717	1.00[a] **1.73 (1.19–2.50)** **1.48 (1.02–2.13)**
Violante[40] 2016	Workers enrolled in the study were full-time employees of seven industrial (tiles, small appliance, large appliances, garment and shoes – two companies – manufacturing) and service organisations (N=3131)	Italy		Unknown	2000-2011	Clinically assessed with NCS	Observation by trained professionals (with videotapes whenever possible)	<AL ≥AL + <TLV ≥TLV	51 36 39 Only cases reported	1.00[a] **1.93 (1.38–2.71)** **1.95 (1.27–3.00)**
Bonfiglioli[24] 2013	A heterogeneous dynamic cohort of persons employed in one of six selected factories [producing large (N=1) and small (N=1) domes-tic appliances, underwear (N=1), ceramic tiles (N=1) and shoes (N=2)] and workers employed in all municipal nursery schools of Bologna (N=2194).	Italy		1349 (61.5%)	2000-2003	Clinically assessed with NCS	Blinded walk-through inspection by trained professionals	<AL ≥AL + <TLV ≥TLV	34/1235 24/518 26/442	**Incident rate ratio:** 1.00[a] **1.95 (1.21–3.16)** **2.70 (1.48–4.91)**
Burt[25] 2013	Three worksites: a hospital, a school bus manufacturing plant and an engine assembly plant. (N=347)	United States		146 (42.1%)	2-year follow-up	Clinically assessed with NCS	Observation on-site and videotaped	<AL ≥AL + <TLV ≥TLV	5/102 1/10 23/235	1.00 2.16 (0.23-20.51)* 2.10 (0.78-5.70)*

Violante[39] 2007	A heterogeneous dynamic cohort of persons employed in one of six selected factories [producing large (N=1) and small (N=1) domes-tic appliances, underwear (N=1), ceramic tiles (N=1) and shoes (N=2)] and workers employed in all municipal nursery schools of Bologna (N=2092)	Italy		1356 (64.8%)	1-year follow-up	Clinically assessed without NCS	Preliminary walk-through surveys	<AL ≥AL + <TLV ≥TLV	63/1009 25/333 65/418	1.00 1.50 (0.90–2.50) **3.00 (2.00–4.50)**
Garg[27] 2012	Workers were recruited from 10 diverse production facilities. Workers at these facilities performed a variety of operations including: (i) poultry processing, (ii) manufacturing and assembly of animal laboratory testing equipment, (iii) small engine manufacturing and assembly, (iv) small electric motor manufacturing and assembly, (v) commercial lighting assembly and warehousing, (vi) electrical generator manufacturing and assembly, (vii) metal automotive engine parts manufacturing and (viii) plastic and rubber automotive	Unites States		272 63.4%	6-year follow-up	Clinically assessed with NCS	Observation by trained professionals (with videotapes whenever possible) and interviews	<AL ≥AL + <TLV ≥TLV	7/98 12/160 16/171	1.00[a] 1.44 (0.55–3.76) 2.01 (0.80–5.04)

	engine parts manufacturing and assembly (N=429)									
Repetition										
Dale[26] 2018	The study cohort consisted of pooled data from six prospective studies. Participants were full-time employees, 18 years of age or older, who performed hand-intensive activities, and were employed in industries such as manufacturing, production, service and construction (N=2393)	United States		1249 (52,2%)	2.8-year follow-up	Clinically assessed with NCS	Observations and measurements at the worksite by trained observers and detailed video analysis of the worker performing their tasks	HAL <4.5 HAL >4.5	Not given	1.00[b] 1.28 (0.90-1.83)
Harris-Adamson[29] 2016	Participants in four different prospective studies were at least 18 years of age (N=1605)	United States		717 (45.0%)	3.5-year follow-up	Clinically assessed with NCS	Blinded trained analyst's observation of each participant per-forming his/her usual work tasks, measurement of hand forces, weights of tools, force matching required to complete each task, videotape analysis and interviews	HAL ≤4.4 HAL >4.4	41 49 Only cases reported	1.00[b] **1.90 (1.17-3.10)**
Harris-Adamson[28] 2015	The pooled study cohort consisted of data from five research groups. Participants in all studies were at least 18 years of age (N=3214)	United States		1274 (39.6%)	6.5-year follow-up	Clinically assessed with NCS	Videotape analysis, interviews and measurements	HAL ≤4 HAL >4 - ≤5.3 HAL >5.3	59 48 57 Only cases reported	1.00[b] **1.54 (1.02-2.32)** 1.32 (0.87-2.02)

Violante[40] 2016	Workers enrolled in the study were full-time employees of seven industrial (tiles, small appliance, large appliances, garment and shoes – two companies – manufacturing) and service organisations (N=3131)	Italy		Unknown	2000-2011	Clinically assessed with NCS	Observation (with videotapes whenever possible) and was complemented, where available, by standard production times and data by a team of trained professionals	HAL 1.0-3.0 HAL 3.1-5.0 HAL 5.1-8.5	44 60 22 Only cases reported	1.00[a] **2.06 (1.61–2.65)** **2.06 (1.37–3.09)**
	Force duration									
Burt[25] 2013	Three worksites were selected: a hospital, a school bus manufacturing plant and an engine assembly plant. (N=347)	United States		146 (42.1%)	2-year follow-up	Clinically assessed with NCS	Observation on-site and videotaped	Force duration <20% ≥20% - <60% >60%	 10/216 14/112 5/13	 1.00 **2.83 (1.18-6.79)** **9.57 (5.96-64.24)**
Dale[26] 2015	The study cohort consisted of pooled data from six prospective studies. Participants were full-time employees, 18 years of age or older, who performed hand-intensive activities, and were employed in industries such as manufacturing,	United States		1249 (52,2%)	2.8-year follow-up	Clinically assessed with NCS	Observations and measurements at the worksite by trained observers and detailed video analysis of the worker performing their tasks	Force duration <16.38% >16.38%	Not given	 1.00[b] **1.74 (1.38-2.20)**

	production, service and construction (N=2393)									
Harris-Adamson[28] 2015	The pooled study cohort consisted of data from five research groups. Participants in all studies were at least 18 years of age, employed at a company where some workers performed hand-intensive activities (N=3214)	United States		1274 (39.6%)	6.5-year follow-up	Clinically assessed with NCS	Videotape analysis, interviews and measurements	Force duration ≤11% >11% - ≤32% >32%	 56 53 57 Only cases reported	 1.00[b] 1.46 (0.98-2.17) **2.05 (1.34-3.15)**
Harris-Adamson[29] 2016	Participants in four different prospective studies were at least 18 years of age (N=1605)	United States		717 (45.0%)	3.5-year follow-up	Clinically assessed with NCS	Blinded trained analyst's observation of each participant per-forming his/her usual work tasks, measurement of hand forces, weights of tools, force matching required to complete each task, videotape analysis and interviews	Force duration ≤11% >11% - ≤32% >32%	 56 53 57 Only cases reported	 1.00[b] 1.46 (0.98-2.17) **2.05 (1.34-3.15)**
Hand-arm vibration										
Hulkkonen[30] 2020	The study population consisted of the Northern Finland Birth Cohort of 1966 (NFBC1966) who were working ≥3 days a week in a paid job and answered the postal questionnaire on work-related factors (N=6326)	Finland		3066 (48.5%)	31-year follow-up	Clinically assessed without NCS	Questionnaire	None or light Moderate or high	185/5858 30/468	1.00[c] **3.32 (2.19–5.03)**
Pourmemari[37] 2018	A representative sample of men and women aged 30 years or older living in Finland between the fall 2000 and spring 2001 was recruited	Finland		3353 (54.3%)	11-year follow-up	Clinically assessed without NCS	Interviews	No vibration tools Using vibration tools	103/5489 10/589	1.00[c] 0.90 (0.5-1.90)

	using a two stage cluster sampling design (N=6177)									
Nathan[36] 2005	A group of Portland, Oregon, area industrial workers first examined in 1984 (N=471)	United States		188 (40.0%)	1984-2001	Clinically assessed with NCS	Observation of job tasks	No vibration tools Using vibration tools	Not given	Odds ratio: 1.00 2.15 (not given) P-value = 0.33
Harris-Adamson[28] 2015	The pooled study cohort consisted of data from five research groups. Participants in all studies were at least 18 years of age, employed at a company where some workers performed hand-intensive activities (N=3214)	United States		1274 (39.6%)	6.5-year follow-up	Clinically assessed with NCS	Videotape analysis, interviews and measurements	No vibration tools Using vibration tools	82 57 Only cases reported	1.00[b] 1.04 (0.69-1.55)
	Force intensity									
Dale[26] 2015	The study cohort consisted of pooled data from six prospective studies. Participants were full-time employees, 18 years of age or older, who performed hand-intensive activities, and were employed in industries such as manufacturing, production, service and construction (N=2393)	United States		1249 (52,2%)	2.8-year follow-up	Clinically assessed with NCS	Observations and measurements at the worksite by trained observers and detailed video analysis of the worker performing their tasks	Borg CR-10 scale ≤3 >3	Not given	1.00[b] **1.38 (1.06-1.80)**
Harris-Adamson[28] 2015	The pooled study cohort consisted of data from five research groups. Participants in all studies were at least 18 years of age, employed at a company where some workers performed hand-intensive activities (N=3214)	United States		1274 (39.6%)	6.5-year follow-up	Clinically assessed with NCS	Videotape analysis, interviews and measurements	Borg CR-10 scale ≤2.5 >2.5 - ≤4 >4	49 65 39	1.00[b] **1.59 (1.09-2.34)** **2.17 (1.38-3.43)**

									Only cases reported	
Harris-Adamson[29] 2016	Participants in four different prospective studies were at least 18 years of age (N=1605)	United States		717 (45.0%)	3.5-year follow-up	Clinically assessed with NCS	Blinded trained analyst's observation of each participant per-forming his/her usual work tasks, measurement of hand forces, weights of tools, force matching required to complete each task, videotape analysis and interviews	Borg CR-10 scale ≤3 >3	 42 37 Only cases reported	 1.00[b] 1.38 (0.85-2.26)
Violante[40] 2016	Workers enrolled in the study were full-time employees of seven industrial (tiles, small appliance, large appliances, garment and shoes – two companies – manufacturing) and service organisations (N=3131)	Italy		Unknown	2000-2011	Clinically assessed with NCS	Observation by trained professionals (with videotapes whenever possible)	Borg CR-10 scale 1.0-3.0 3.1-5.0 5.1-7.0	 18 86 22 Only cases reported	 1.00[a] 1.68 (0.87–3.23) **2.62 (1.63–4.21)**
Leclerc[33] 2001	Workers were exposed to repetitive work in one of the following five activity sectors: (i) assembly line in the manufacture of small electrical appliances, motor vehicle accessories, or ski accessories (packaging excluded), (ii) clothing and shoe industry (packaging excluded), (iii) food industry (mainly, meat industry), packaging excluded, (iv) packaging (primarily in the food industry), (v) supermarket cashiering (N=158)	France		Only men were included	3-year follow-up	Clinically assessed without NCS	Questionnaire	 No Yes	Not given	Odds ratio: 1.00 **4.09 (1.43-11.70)**

Lund[34] 2019	a cohort of Danish citizens born 1940–1979 (18-80 year-olds) within 30 different jobs (N=1,015,418)	Denmark		583,370 (57.5%)	1992-2015	Clinically assessed without NCS	Measurements of movements and position of the wrist using representative whole day electro-gonio-metrical measurement	Mean power frequency, Hz <0.001≤ – <0.23 0.23≤ – 0.24 0.24≤ – 0.27 0.27≤ – 0.29 0.29≤ – 0.45	897 1117 1068 1941 1811 Only cases reported	**Incident rate ratio:** 1.00[a] 0.78 (0.72-0.86) **1.51 (1.37-1.66)** **1.33 (1.23-1.44)** **1.83 (1.68-1.98)**
	Wrist bending posture									
Roquelaure[38] 2020	A large sample of workers in the French Pays de la Loire (N=1367)	France		563 (41.2%)	5-year follow-up	Clinically assessed without NCS	A self-administered questionnaire	Never 2 to 4 hours a day >4 hours a day	20/678 13/278 8/169	1.00 1.61 (0.79-3.29)* 1.63 (0.70-3.78)*
Harris-Adamson[28] 2015	The pooled study cohort consisted of data from five research groups. Participants in all studies were at least 18 years of age, employed at a company where some workers performed hand-intensive activities (N=3214)	United States		1274 (39.6%)	6.5-year follow-up	Clinically assessed with NCS	Videotape analysis, interviews and measurements	Time≥30°wrist **extension**: ≤5% >5% Time≥30°wrist **flexion**:	Only cases reported 88 65	1.00[b] 0.87 (0.59-1.29)

								≤1% >1%	83 70	1.00[b] 0.83 (0.60-1.15)
Holding tools/objects in a pinch grip										
Roquelaure[38] 2020	A large sample of workers in the French Pays de la Loire (N=1367)	France		563 (41.2%)	5-year follow-up	Clinically assessed without NCS	A self-administered questionnaire	Never pinch gripping 2 to 4 hours a day >4 hours a day	31/958 6/147 8/108	1.00 1.27 (0.52-3.10)* **2.39 (1.07-5.34)***
Pourmemari[37] 2018	A representative sample of men and women aged 30 years or older living in Finland between the fall 2000 and spring 2001 was recruited using a two-stage cluster sampling design (N=6177)	Finland		3353 (54.3%)	11-year follow-up	Clinically assessed without NCS	Interviews	Not pinch gripping Pinch gripping	76/4305 37/1767	1.00[c] 1.20 (0.80-1.90)
Leclerc[33] 2001	Workers were exposed to work in one of the following five activity sectors: (i) assembly line in the manufacture of small electrical appliances, motor vehicle accessories, or ski accessories (packaging excluded), (ii) clothing and shoe industry (packaging excluded), (iii) food industry (mainly, meat industry), packaging excluded, (iv) packaging (primarily in the food industry), (v) supermarket cashiering (N=158)	France		Only men were included	3-year follow-up	Clinically assessed without NCS	Questionnaire	Not pinch gripping Pinch gripping	Not given	Odds ratio: 1.00 **3.59 (1.06-12.10)**

	Computer/keyboard use									
Mediouni[35] 2015	The Cosali cohort: Workers from the Loire Valley area of West Central France. This area represents 5.6% of the French workforce (N=1551)	France		658 (42.4%)	2007-2010	Clinically assessed without NCS	A self-administered questionnaire	Never/almost never <2 hours a day 2 to 4 hours a day All/almost all day	22/611 5/234 1/219 8/482	1.00[a] 0.60 (0.22-1.63) 0.13 (0.02-1.01) **0.39 (0.17-0.89)**
	The prediCTS cohort: Newly employed workers from eight companies and three construction trade unions in the St Louis region of the USA (N=711)	United States		253 (35.6%)	2007-2011	Clinically assessed with NCS	Job exposure matrix	Never/almost never <2 hours a day 2 to 4 hours a day All/almost all day	23/355 2/77 1/52 3/202	1.00[a] 0.38 (0.09-1.67) 0.20 (0.03-1.62) **0.16 (0.05-0.59)**
Nathan[36] 2005	A group of Portland, Oregon, area industrial workers first examined in 1984 (N=471)	United States		188 (40.0%)	1984-2001	Clinically assessed with NCS	Observation of job tasks	 ≤1 hour a day >1 hour a day	Not given	Odds ratio: 1.00 0.81 (not given) P-value = 0.39
	Revised Strain Index (RSI)									

Kapellusch[31] 2021	Participants were recruited among voluntary workers performing diverse jobs in different industries (N=1372)	United States		798 (58.2%)	2.5-year follow-up	Clinically assessed with NCS	Blinded videotape analysis, interviews and task measurements	RSI ≤ 10 RSI > 10	68/674 89/698	1.00[d] **1.45 (1.11-1.91)**
Garg[27] 2012	Workers were recruited from 10 diverse production facilities. Workers at these facilities performed a variety of operations including: (i) poultry processing, (ii) manufacturing and assembly of animal laboratory testing equipment, (iii) small engine manufacturing and assembly, (iv) small electric motor manufacturing and assembly, (v) commercial lighting assembly and warehousing, (vi) electrical generator manufacturing and assembly, (vii) metal automotive engine parts manufacturing and (viii) plastic and rubber automotive engine parts manufacturing and assembly (N=429)	United States		272 63.4%	6-year follow-up	Clinically assessed with NCS	Observation by trained professionals (with videotapes whenever possible) and interviews	RSI ≤ 6.1 RSI > 6.1	6/121 29/308	1.00[a] **2.48 (1.00–6.13)**

*HR was calculated by authors
[a]adjusted for sex, age, body mass index, predisposing diseases
[b]adjusted for sex, age, body mass index, study site
[c]adjusted for sex
[d]adjusted for sex, age, body mass index

AL: Action Limit
TLV: Threshold Limit Values
NCS: nerve conduction study
HAL: Hand Activity Level
RSI: Revised Strain Index

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