2024

The association between occupational mechanical exposures and Dupuytren's disease: a reference document

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Foreword

In Denmark, it is conceivable that Dupuytren's disease, resulting from prolonged exposure of work with powerful vibrating tools, might be considered as a potential occupational disease. Due to new scientific studies, the Danish Labour Market Insurance and the Occupational Diseases Committee have requested a reference document to re-evaluate the existing guidelines of the exposure requirements in relation to occupational mechanical exposures. A reference document was conducted in form of a systematic review and meta-analysis to study the association between occupational mechanical exposures and Dupuytren's disease.

The reference document was conducted by research assistant Alexander Jahn, professor Johan Hviid Andersen, professor Alexis Descatha, and associate professor Annett Dalbøge. Professor Torben Bæk Hansen and Professor Lars Dahlin independently evaluated the reference document. The reference document was funded by The Danish Work Environment Research Fund with grant no 30-2022-09 20225100752.

Contents

1. Introduction

Dupuytren's disease (DD), named after the French surgeon Guillaume Dupuytren, is a progressive, irreversible disease affecting the connective tissue of the palm and fingers. The condition leads to the formation of abnormal collagen deposits in the palmar fascia, an aponeurotic sheet lying deep into the dermis and superficial to the flexor tendons of the hand.[1] Here, fibromatous nodules form in the superficial fibres of the fascia, making the nodules visible under the dermis. The nodules are firm and sometimes painful for the patient and precede the development of a cord formation. The disease accumulates over time and the cord gradually contracts, adhering to the dermis, leading to deformity of the affected finger. The metacarpophalangeal (MCP), the proximal interphalangeal (PIP) joint, and to a lesser degree, the distal interphalangeal (DIP) joint of the affected finger pull towards the palm, most commonly affecting the 4th and 5th fingers, impairing the overall function of the hand.[1-3] Additionally, many individuals encounter challenges with thumb movement due to contraction. Consequently, this deformity leaves the hand with a diminished function, limiting the workability and everyday activities.

The DD diagnose is classified in the International Classification of Disease, 10th version (ICD-10) under M72 (Fibroblastic disorders), subclassified in M72.0 (Palmar Fascial Fibromatosis, Dupuytren). The diagnosis is based on clinical symptoms, hand injury history, and medical history. The clinical symptoms are characterised by thickening of the fibrous bands of the palmar fascia, formation of fibromatous nodules, and flexion contractures of the MCP or PIP joints.

Dupuytren's disease can be treated through surgical and non-surgical methods, often leading to functional improvement of the affected hand. Non-surgical options depend on the disease's progression and include steroid injection, collagenase injection (enzymatic fasciotomy), and needle aponeurotomy.[1 4] If surgery is considered, common procedures include fasciotomy (removing involved fascia) or partial palmar fasciectomy (division of contracted fascia).[1 4] In cases of recurrence, a more extensive dermo-fasciectomy, involving both skin and fascia removal, might be considered, and finally, in severe, recurrent cases, amputation can be performed.[5]

Recurrence of DD is common and has been estimated to vary between approximately 20% and up to more than 80%, depending on the method of treatment surgery, length of time since treatment, histological type, and discriminating between recurrence (appearance of DD in an area already cleared by surgery) and extension (appearance of DD in an unoperated area).[6-11]

It is estimated that 8.2% of the global population is affected by the condition,[12] but the prevalence varies significantly between age groups and geographical locations. A higher prevalence of Dupuytren's disease typically occurs in the elderly population and more often affects elderly men of northern European descent.[13 14] The mean prevalence of DD based on general populations of Western countries was estimated to 12% at age 55, 21% at age 65, and 29% at age 75 determined from 10 studies.[15]

Genetic factors are associated with the pathogenesis of DD,[14 16-20] but individual and environmental factors also seem to increase the risk of developing DD, including alcohol,[1 21-24] smoking,[1 22 23] diabetes,[22 24 25] sex,[2 14] and occupational mechanical exposures.[1 14 22 26-31] Occupational mechanical exposures encompass a range of physical demands that individuals encounter in the work environment such as repetitive movements, forceful exertions, vibrations, and sustained periods of mechanical loadings. The accumulative effect of occupational mechanical exposures placing stress and strain on the hand's tissue has the potential to disrupt repairing processes, causing micro-trauma, trigger inflammation, promote collagen deposition, and the development of contractures. The risk of developing DD among workers exposed to occupational mechanical exposures has been reported in a few reviews, mainly related to vibration exposures.[22 26-30]

In 1996, Liss et al[26] conducted a review examining the relationship between DD and work, including manual work and hand vibration. Seven studies met their inclusion criteria written in English and three non-English studies were identified and translated. In total, ten studies were deemed eligible. Of studies with acceptable quality, one examined the relationship between DD and manual work and three examined the relationship between DD and hand vibration. All found a positive association with at least a doubling of the risk.

In 2011, Descatha et al[27] conducted a systematic review and meta-analysis investigating the association between work exposure and DD. Fourteen studies were deemed eligible for inclusion in the meta-analysis and an odds ratio (OR) of 2.02 (1.57 - 2.60) was found for manual work and an OR of 2.88 (1.36 - 6.07) for vibration at work. Similar ORs were found for each mechanical exposure when repeating the meta-analysis stratified on the methodological quality.

Mathieu et al[28] investigated the association between exposure to vibration and DD in a systematic review from 2020. By including nine studies in the meta-analysis, an OR of 2.87 (1.41 - 5.84) were found among patients with exposure to vibration compared to controls. Comparing demographics between patients and controls, differences in known risk factors of developing DD was observed. Patients with DD were more likely to be older, diagnosed with diabetes, and a higher consumption of alcohol.

Alser et al[22] investigated nongenetic factors associated with DD in a systematic review from 2020. Fourteen studies were identified, of which ten studies showed a positive association. Of these, six studies assessed exposure to heavy manual work, three studies assessed exposure to vibration tools, and one study assessed exposure to repetitive manual work. The remaining four studies found no or inconclusive association between manual work and DD. As the first systematic review of the above-mentioned, Alser et al conducted a level of evidence assessment. A Strong level of evidence was assessed of the association between the history of manual work and DD.

Geoghegan et al[29] conducted a narrative systematic review in 2021, investigating factors associated with the development of DD. Four studies found significant associations between occupation and DD.

Finally, two systematic reviews were published in 2023 of the association between exposure to hand-arm/hand-transmitted vibration and DD. Gerger et al[30] examined the relationship between hand-arm vibration and occurrence of DD. Six studies were included in the meta-analysis, yielding an OR of 1.35 (1.12 - 1.63) of the association between highest level of exposure to vibration and DD. The certainty of the available evidence was considered low.

Nilsson et al[31] examined the association between hand-transmitted vibration and DD. In total, 11 studies were included in the meta-analysis, but they distinguished between studies using not exposed groups or low-exposed groups as references. The meta-analysis comparing exposed vs not exposed yielded an OR of 2.29 (1.60 - 3.27) and the meta-analysis comparing low exposed vs high exposed yielded an OR of 2.16 (1.19 - 3.94).

Of the seven systematic reviews, the majority focused on examining the impact of vibration exposure. Since 2011, there has been no meta-analysis analysing the effects of exposure to manual work. Additionally, only two systematic reviews have evaluated the certainty of evidence.[22 30] Considering that occupational mechanical exposures, beyond just vibration, could potentially be associated to DD, the aim of this systematic review and meta-analysis is to investigate and synthesise the current scientific evidence regarding the association between occupational mechanical exposures, encompassing vibration, and the development of DD.

2. Methods

The reference document was conducted as a systematic review and meta-analysis. We used guidelines stated by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [32] and complied with the AMSTAR (Assessing the Methodological Quality of Systematic Reviews)[33] tool to ensure the methodological quality of our systematic review. Furthermore, the systematic review and meta-analysis complied with specific guidelines for preparation and quality approval provided by the Danish Working Environment Fund. A protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42023433351.

The systematic review and meta-analysis were funded by The Danish Working Environment Research Fund, part of The Ministry of Employment administered by the Danish Working Environment Authority with grant no 30-2022-09 20225100752.

2.1 Literature search

The systematic literature search was designed, tested, and performed in collaboration with a research librarian. The syntax of the literature search was optimised for each specific database and the systematic literature search was performed the 12th and 13th of April 2023 in National Library of Medicine (Medline), Excerpta Medica Database (EMBASE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and Web of Science. No limitations were used regarding year of publication. The search strategy was developed using blocks, each containing MeSH terms and free-text words, and combined with Boolean operators within and between each block. In Appendix 1 the search string for Medline is provided. In addition, the systematic literature search was supplemented with hand-searching references of eligible articles included in our systematic review. Finally, we used the Google Scholar search engine to identify potential articles by screening the first 100 articles.

To screen for eligible articles, all potential articles identified in the systematic literature search was transferred to the review management software Covidence. Before the selection of relevant articles, all duplicates were identified and removed. Afterwards, the screening and selection of relevant articles was carried out by two authors (AD and JHA). Each author independently screened all articles using a two-step screening model. At first, articles were screened based on their title and abstract, followed by a full-text reading. If any disagreement occurred between the two authors, a third author would determine the in- or exclusion of the specific article (AJ).

2.2 Inclusion criteria

The inclusion criteria were developed by using components of the PECOS description (Population, Exposure, Comparison, Outcome, and Study design).

2.2.1 Population

We included studies with a population in or above the working-age with current or former employment, and with no limitations to sex, demographic, or ethnicity.

2.2.2 Exposure

The exposure was defined as occupational mechanical exposures, e.g., hand-transmitted vibration, lifting/carrying loads, repetitive hand movements, or a combination of the aforementioned occupational mechanical exposures. Studies with exposure assessments based on self-report, observations, expert ratings, job exposure matrices (JEMs), technical measures, or hybrid measures (combination of different measures) were included.

2.2.3 Comparison

Comparison was defined as a measure of association between occupational mechanical exposures and DD or one possible to calculate. The measure of association applicable comprised relative risks (RR), odds ratios (OR), hazard ratios (HR), or prevalence ratios (PR). Moreover, a comparison should consist of an exposed vs non/less exposed group.

2.2.4 Outcome

Only outcome defined as Dupuytren's disease (also called Dupuytren's contracture, Morbus Dupuytren, Viking disease, palmar fibromatosis, and Celtic hand), unilateral or bilateral, was included. Dupuytren's disease assessed by the following criteria was included: relevant ICD-codes or diagnosis gathered from, e.g., registers, visible nodules in the palm and/or cordlike structures that extend into the fingers, difficulties in stretching fingers, and self-reporting.

2.2.5 Study design

We only included quantitative epidemiological studies, i.e., cohort, case-control, and cross-sectional studies written in English, Danish, Swedish, or Norwegian.

2.3 Data extraction

The data extraction was divided into a descriptive table and an analytic table. In the descriptive table, information regarding study characteristics (i.e., author, study design, population, outcome definition and assessment, and exposure definition and assessment) was included. In the analytic table, information regarding confounders, all levels of exposure groups, stratifications, and measure of association with its corresponding 95% confidence interval (CI) was included. The data extraction was performed by one author (AJ) and the quality was checked by another author (AD or JHA) to ensure consistency. If any discrepancies occurred, the data extraction was resolved by a third author.

2.4 Risk of bias assessment

The risk of bias assessment was conducted using a tool developed and adapted specific for chronic diseases and applied in several previous systematic reviews.[34-38] The risk of bias tool (Appendix 2) consisted of five major risk domains and three minor risk domains: (I) Study design & selection, (II) Exposure, (III) Outcome, (IV) Enrolment or Non-participants, (V) Analysis method, (VI) Funding, (VII) Chronology, and (VIII) Conflict of interest. Based on ratings from all domains, the overall risk of bias of each included study was rated as either low, moderate, or high risk of bias. A study was considered having low risk of bias if all major domains and at least one minor domain were rated as low risk of bias. For a study to be considered as having moderate risk of bias, four out of five major domains and at least one minor domain should be rated as low risk of bias. All other combinations were considered as high risk of bias.

The risk of bias assessment was performed for each included article independently by two authors (AJ, AD or JHA) and ratings were compared. If any discrepancies occurred between ratings, the risk of bias assessment was discussed with all authors until consensus was reached.

2.5 Statistical analysis

Before conducting the meta-analysis, studies based on identical source populations were identified to avoid including double-counting data in the meta-analysis. Occurrences of identical source populations lead to the exclusion of the article with the highest risk of bias assessment. If both articles received the same risk of bias assessment, the article with the smallest number of participants was excluded. In the meta-analysis, odds ratio (OR) was used as the measure of association. If other measure of association estimates was used in a study, it was considered to be equivalent to an OR if the incidence proportion of the outcome was <10%.[39] In addition, if a study provided sufficient information to calculate an OR but did not present such, we calculated the OR and the corresponding 95% confidence interval (CI).

To analyse the association between occupational mechanical exposures and DD, we included the measure of association of the highest exposure group vs the lowest exposure group to ensure exposure contrast. Therefore, in the meta-analysis, we chose measure of associations based on (I) high contrast between exposure groups, (II) the most adjusted measure of association, (III) the measure of association containing most participants, and (IV) comparable measures of association.

For each occupational mechanical exposure, pooled estimates were calculated using random-effects model assuming that the true effect can vary from study to study not only due to random error but differences in heterogeneity.[40 41] Heterogeneity between studies was estimated using I^2 statistics describing the proportion of observed variance that reflects real differences among studies rather than on random error. I^2 was quantified using the restricted maximum likelihood method (REML) and was interpreted by the thresholds:[40]

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Publication bias was evaluated using funnel plots and the asymmetry of the funnel plot was tested by Egger's test. Exposure-response relations were examined by extracting results from statistical test (e.g., trend tests) provided in a study. If an exposure-response relation was not statistically examined, we constructed scatter plots including the risk estimates and 95% CI for each level of exposure from studies providing >3 exposure groups to graphically indicate whether an exposure-response relation existed.

Sensitivity analyses were conducted by repeating the meta-analyses stratifying studies according to low/moderate vs high risk of bias in order to evaluate the effect of risk of bias in the measure of an association. All analyses were performed using STATA 17.0 (Stata corp. College Station, TX, USA).

2.6 Evidence of an association

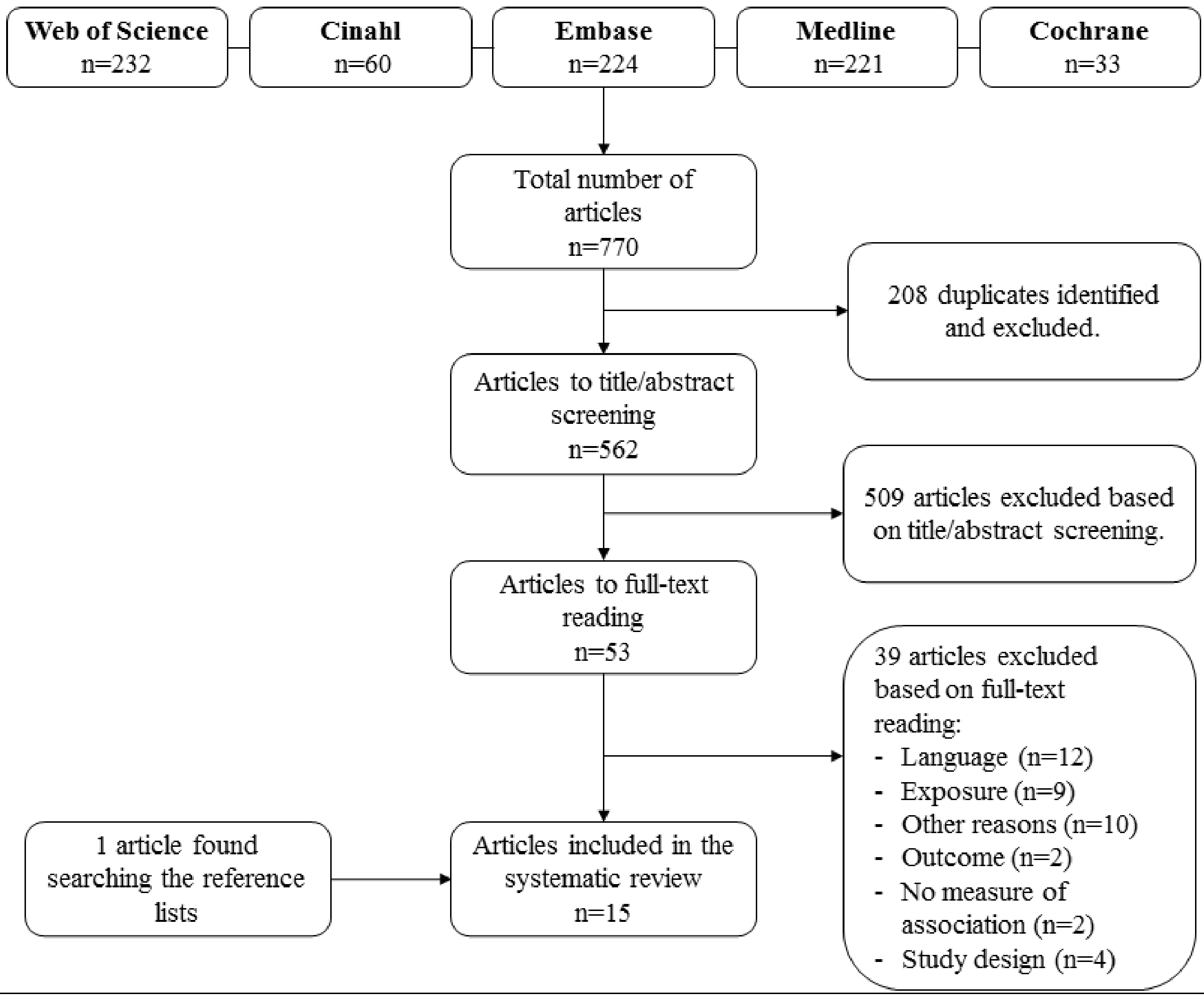
The evidence of a causal association between occupational mechanical exposures and DD was assessed according to guidelines provided by The Danish Work Environmental Fund (Appendix 3). The quality of evidence could be rated as strong (+++), moderate (++), limited (+), insufficient (0), or evidence suggesting lack of a causal association (-). Strong evidence of an association was rated when "A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding." The assessment was performed independently by two reviewers (AJ and JHA), and further discussed by all authors until consensus.

3. Results

3.1 Study selection

Figure 1 presents the inclusion and exclusion of relevant articles identified from the systematic literature search. The literature search yielded 770 articles identified in five scientific databases. After identification of 208 duplicates, 562 articles were screened based on their title and abstract providing 54 articles for full-text reading. After the full-text reading, 15 articles were deemed eligible for inclusion in the systematic review. Additionally, one article was found by searching the reference lists of the included articles. The reasons for exclusion based on the full-text reading are provided in Appendix 4.

Figure 1. Flow chart of the inclusion of articles.



Abbreviations: n=numbers.

3.2 Study characteristics

Table 1 summarises the descriptive characteristics of each of the 15 included articles.[23 42-55] The epidemiological study design of the included articles consisted of 10 cross-sectional studies,[42-45 48 49 51-54] three case-control studies,[47 50 55] and two cohort studies.[23 46] The outcome was assessed using clinical examination in nine studies,[42-45 47 48 50 51 53] questionnaires in two studies,[23 52] register-based information in one study,[46] and register-based information combined with self-reports in one study.[54] One study used clinical examination but with no information given about diagnostic criteria,[49] and one study did not provide any information regarding the outcome assessment.[55]

Information on occupational mechanical exposures were assessed using questionnaires in five studies,[23 45 50 52 53] interview in three studies,[42 43 48] questionnaire followed by an interview in two studies,[47 54] observation of participant's workplace in one study,[51] records of occupation in one study,[49] a job-exposure matrix combined with a questionnaire in one study,[46] and two studies did not provide information of the exposure assessment.[44 55]

Studies were conducted in France,[23 45 46 48] Great Britain,[43 52-54] Italy,[42 50] Norway,[49] Canada,[47] Slovak Republic,[51 55] and India.[44] The studies were published between 1978 and 2023.

Table 1. Characteristics of the 15 included studies. Abbreviations is explained in the footnote.

Author	Design	Study population	Exposure		Outcome	
			Definition	Assessment	Definition	Assessment
Bovenzi et al 1994[42]	Cross-sectional.	The study population comprised 828 stone workers employed in nine districts of North and Central Italy. The exposed participants were grouped into quarry drillers (N=145), stone carvers that were grouped into group A (N=188, only rotary tools) and B (N=237, both rotary and percussive tools). The remaining 258 stone workers formed the control group, consisting of manual polishers and machine operators not exposed to hand transmitted vibrations.	Participants reported detailed description of hand-held power tools used during their career. Usage of vibrating tools was expressed in terms of operating hours/day, days/years, and total years separately for each tool and a lifetime dose was calculated: $= (\Sigma (a_{hW}^2 * t_h)^{0\text{-}5} * t_d * t_y)^2$ m^2h^3/s^4 - a_{hW} is the frequency weighted acceleration measured on the vibrating tools (m/s^2), - t_h is the individually estimated daily exposure (h/day), - t_d is the number of working days/y, and - t_d, is the number of years during which the tool was used.	Interview.	Questions concerning the worker's history of musculoskeletal disorders such as DD were asked during the clinical examination. No further explanation is given.	Clinical examination and interview.
Burke et al 2007[43]	Cross-sectional.	The study population comprised 97,537 British miners seeking compensation for Hand-Arm Vibration Syndrome.	Vibration was assessed as how many years the claimants had been exposed to vibrating tools at their employment in any industry.	Interview.	The clinical examination was carried out by doctors and included assessment of thickening of the palmar fascia to established contractures.	Clinical examination.
Dasgupta et al 1996[44]	Cross-sectional.	The study population comprised 66 miners using jackhammers (mean age of 37.5 years) from two limestone mines in India and 35 blasters who did not used vibrating tools (mean age of 42.3 years).	Exposed to vibration (operating a jackhammer at work).	Not stated.	The clinical examination assessed for signs of vascular disorders, neuropathy, and musculoskeletal abnormalities. The diagnose of DD was found based on the clinical evidence.	Clinical examination.

Descatha et al 2012[45]	Cross-sectional.	The study was conducted in Pays de la Loire region in west-central France. The study population comprised 2161 men aged 20 to 59 years and employed in the private sector, self-employed, civil servants, and public sector employees.	Information on use of vibrating tools and manual work (any hand tool + vibrating tools) was based on information on the characteristics of the job and tasks in a typical working day in the preceding 12 months.	Questionnaire.	A subject was considered as having Dupuytren's disease if the occupational physician found incomplete extension of the phalanx, permanent flexion deformity or fibrous nodules in one of the 4 fingers.	Clinical examination.
Descatha et al 2014[23]	Cohort.	The study population comprised 13,587 participants (10,017 men with a mean age of 68 years and 3570 women with a mean age of 65 years) working at the French national utility for energy production and distribution. Participants was included if they answered the 2012 questionnaire.	Questions regarding number of years of exposure (e.g., carrying loads and manipulating vibrating tools) during their working lives were gathered.	Questionnaire.	A specific question on Dupuytren's disease was asked: "(1) Have you ever had Dupuytren's disease (thickening of the palmar skin, nodes, or contracture of the fourth finger of the hand)? (2) if yes, do you have any limitations because of it? (3) Have you had surgery for it?"	Questionnaire.
Fadel et al 2019[46]	Cohort.	All participants were included in the CONSTANCES population-based cohort covered by the French National Health Insurance. Analysing exposure to forearm rotation and usage of vibration tool, the study population comprised 23,795 participants (11,284 men and 12,511 women) with an average age of 52.6 years. Analysing exposure to arduous work or carrying heavy loads, the study.	Exposure to forearm rotation and usage of vibrating tools was evaluated using a JEM rating the participant's exposure from 0 (never or almost never) to 3 (almost always) based on work history. Exposure to arduous work or carrying heavy loads was based on the duration of exposure divided into no exposure, >0 and <10 years, $\geq$10 and <20 years, and $\geq$20 years.	Job-exposure matrix and questionnaire.	Surgery for DD (including palmar or digital fasciotomy and percutaneous needle fasciotomy) was gathered from the National Health Administrative database containing information on all residents in France affiliated with the French National Health Insurance.	Register data.

		population comprised 81,801 participants (38,736 men and 43,065 women).				
Haines et al 2017[47]	Case-control.	Cases (N=129 whereas 98 was men) referred to the nine plastic surgeons in Hamilton, Ontario, Canada, treated or had surgery for DD with a mean age of 56.2 years. Controls with sebaceous cysts were selected from the same plastic surgical practices (N=74) and from the general population (N=106) residing in Hamilton (N=83 men) with a mean age of 51.9 years.	Information on repetitive handwork, heavy handwork, and vibrating tools was gathered from interviews following the questionnaire. Frequency for repetitive handwork was measured from 0-10 (hands idle most of the time, no regular exertion to rapid steady exertion/motion, no pauses, difficulty keeping up). Intensity for heavy handwork and vibration was measured from 0-10 (none to extreme). Finally, subjects were asked to estimate the numbers of hours per day, week, and year that they spent doing repetitive handwork, heavy handwork, or using vibrating power tools in the job. This was itemised for all jobs held by the participant for more than 1 year.	Questionnaire followed by an interview.	Surgeons identified current cases diagnosed with either flexion contracture of the MCP or PIP joints caused by palmar or digital cords not associated with scar contractures or congenital camptodactyly, or palmar or digital nodules or cords or skin tethering, without contracture at the MCP or PIP joint.	Clinical examination.
Hnanicek et al. 2008[55]	Case- control.	Cases consisted of 90 unselected patients undergoing surgery for DD and being of Caucasian descent (82 men and 8 women). Cases had a mean age of 60.6 (SD 9.7) years. The control group consisted of 33 subjects with a mean age of 56 (SD 16.3) years, including the same ethnic background and comparable of age, sex ratio and BMI as the case group. Controls were recruited from Prague and the central.	History of long-term strenuous manual work was defined as >5 years.	Not stated.	No information is provided about how DD was defined, in which surgery unit cases were drawn, or how DD was examined. Controls underwent a routine physical examination by a general practitioner or internist.	Not stated.

		Bohemia region of the Czech Republic.				
Lucas et al 2008[48]	Cross-sectional.	The study population comprised 2406 civil servants seen in 1998 and living in the region of Pays de la Loire and Brittany, France. Participants included all that attended occupational physicians working at the Ministry of Equipment in these regions.	Occupational mechanical exposures were: 1) Using a tool with handle, 2) using a vibrating tool, 3) manual handling, and 4) repairing mechanical equipment. For all exposures, information on how many years, and how many months for each year was gathered grouped into <1 month, 1-6 months, and ≥6 months.	Interview.	Occupational physicians looked for clinical signs of thickening of the palmar fascia and/or flexion contracture in phalanx 2,3,4 or 5.	Clinical examination.
Mikkelsen et al 1978[49]	Cross-sectional.	The study population comprised 15,950 persons living in the municipality of Haugsund, Norway, in 1969.	Occupations were divided into four categories: - Heavy manual work (e.g., lumberjacks, full time farmers) - Medium heavy work (e.g., bricklayers, most of the mechanics), - Light manual work (e.g., dentists, most industrial workers), - No manual work (e.g., clerks, vicars).	Records of occupation.	No information is given about the diagnostic criteria used to determine DD, but all participants was examined for DD.	Examination (NS).
Morelli et al 2017[50]	Case-control.	The study population comprised 59 cases (45 men and 14 women, mean age of 65.4 years) admitted to San Raffaele Hospital, Milano, Italy, in the Orthopaedics and Trauma Surgery Department. Controls (N=104, mean age of 59.4 years)) were matched on age and sex reaching the Orthopaedics and Trauma Department for traumatic reasons (not DD). Possible unrecognised DD were examined before the controls	Occupational mechanical exposures were assessed with two questions: 1) "Do you perform any heavy manual work during the day? How often?" and 2) "How often do you use vibrating tools" with the following answers: Never, not daily, daily (less than 2 hours), and daily (more than 2 hours).	Questionnaire.	DD was assessed during a clinical examination upon admitting to the Orthopaedic and Trauma Surgery Department.	Clinical examination.

		were enrolled in the study.				
Murinova et al 2021[51]	Cross-sectional.	The study population comprised of 515 men (mean age of 50.5 yeas) listed in the database of Department of Occupational Medicine and Clinical Toxicology, Slovak Republic.	Information on hand-transmitted vibrations and heavy manual work was obtained from hygiene monitoring of participant's workplaces. Daily exposure to vibrations was assessed for 8-h energy equivalents of frequency-weighted acceleration. Workers who exceeded 2.5 m/s^2 were considered exposed. Heavy manual work in the occupational environment was defined as one or more tasks that separately or together could overload the employee´s musculoskeletal system. Work was considered excessive when applied muscle strength is above 15% of a worker's maximum muscle strength.	Observation of workplaces.	The clinical diagnose of DD was made by occupational physicians from the Department of Occupational medicine and Clinical Toxicology. Criteria was an incomplete extension of the phalanx, a permanent flexion deformity or if fibrotic nodules in the palm was present.	Clinical examination.
Palmer et al 2014[52]	Cross-sectional.	The study population comprised 4969 men aged between 16 to 65 years selected at random from patient lists of 34 general practices, and members of the armed services chosen at random from central military pay records in Great Britain.	Information on occupational mechanical exposures were gathered from questions regarding: 1) exposures to hand-transmitted vibrations at work in the previous 7 days, 2) exposure to hand-transmitted vibrations in previous paid jobs for >1 hour/week, 3) physical activities in a typical workday (lifting weights roughly 25 kg), digging or shovelling, and use of computer keyboard for >4 hours/day. Exposure to hand-transmitted vibrations was obtained principally from a question about use in the past week of 39 listed tools and machines and an average personal daily vibrations exposure for the past week was calculated.	Questionnaire.	DD was assessed by means of a single question: "Is your little finger (or little and ring finger) of either hand permanently bent as shown opposite so that you cannot straighten it, even with the other hand?" The question was accompanied by a line drawing.	Questionnaire.

Thomas and Clarke 1992[53]	Cross-sectional.	The study population comprised 500 (499 men and 1 woman) claimants, mainly industry workers, in Great Britain with age ranging from 25 to 85 years considering having vibration white finger. The control group consisted of 150 men between 50 to 85 years of age, who were examined for the presence or absence of DD following admission for elective or emergency treatment to a general surgical ward at Middlesbrough General Hospital. Of the 150 controls, 102 performed heavy manual labour, 29 were clerks, teachers, shop assistants etc., the remaining 19 had varying semi-skilled or unskilled occupations.	Standardised questionnaire consisting of full occupational history was used. Information on years exposed to vibrating tools was gathered for the claimants.	Questionnaire.	Clinical examination where all stages of DD were included, from a single palmar nodule to advanced flexion contractures.	Clinical examination.
Van den Berge et al 2023[54]	Cross-sectional.**	Only white British people were selected for this study population. Data was drawn from the UK Biobank. After exclusion, 126,880 participants were included in the work analysis and 58,936 were included in the exposure-response analysis. The mean age of the manual work analysis was 52.7 years for exposed participants and 52.8 years for unexposed participants in the propensity matched group.	At recruitment, manual work status was assessed by participant's current employment by answering whether their current job involves manual or physical work: Rarely, sometimes, usually, or always. Information on cumulative manual work was gathered using the Occupational Information Network (O*NET) containing information of physical requirements of nearly 1000 occupations. UK occupational classification was linked to a US occupational classification in order	Self-completed questionnaire and computer-assisted interview.	DD was identified based on ICD-10 codes, Office of Population Censuses and Services-4 code for DD surgery, self-reported DD at recruitment.	Registry and self-report.

	The mean age of the exposure-response analysis was 53.3 for both exposed and the unexposed participants.	to use the O*NET manual work exposure estimates and three relevant manual work questions from the O*NET database was identified and used.	

Abbreviations: DD = Dupuytren's disease, kg = kilogram, ICD = International classification of diseases, MCP = metacarpophalangeal, N = number, NS = not stated, PIP = proximal interphalangeal, UK = United Kingdom.

** The assessment of the study design is based on the authors understanding of the article. The study design has been discussed independently among a group of researchers until consensus, reflecting the authors' opinion.

3.3 Risk of bias assessment

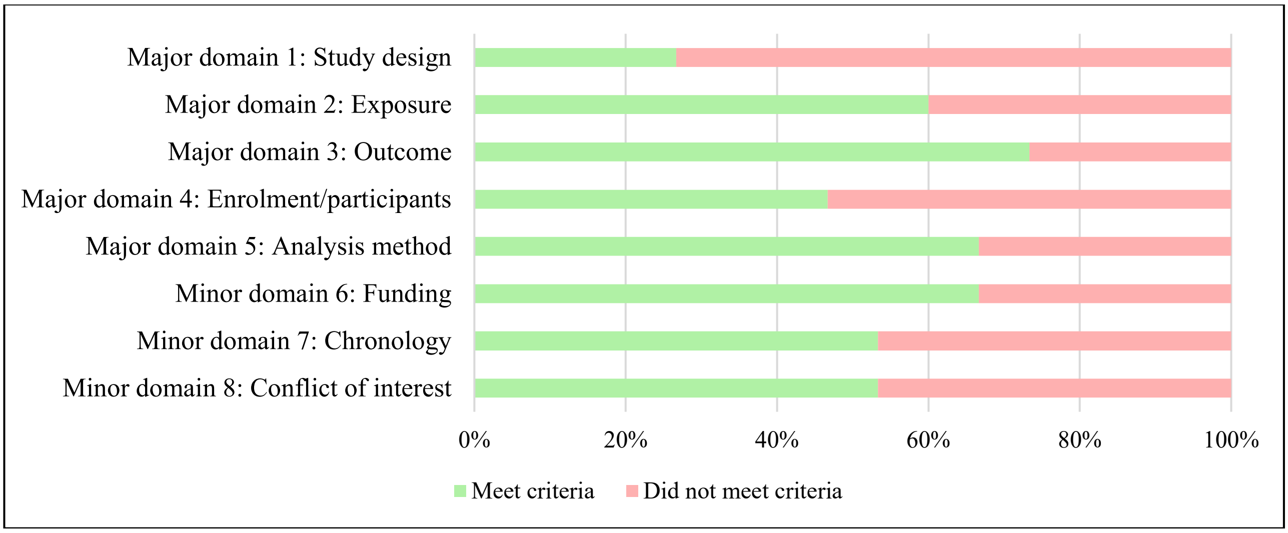
The risk of bias assessment is presented in Table 2 and the summaries are presented in Figure 2. Five studies were assessed as having a moderate risk of bias and 10 studies were assessed as having a high risk of bias. No studies were assessed as having a low risk of bias. The most frequent major domain receiving a low risk of bias assessment was "*Outcome*" and "*Analysis method*". Conversely, the most frequent major domain rated with a high risk of bias was "*Study design*" followed by "*Enrolment/participants*".

Table 2. Risk of bias assessment of the 15 included studies.

References	Quality score	Domains							
		Major					Minor		
		1	2	3	4	5	6	7	8
Bovenzi et al. 1994[42]	Moderate risk	✓	✓	×	✓	✓	×	✓	?
Burke 2007[43]	Moderate risk	×	✓	✓	✓	✓	×	✓	?
Dasgupta et al. 1996[44]	High risk	×	×	×	✓	×	×	✓	?
Descatha et al. 2012[45]	Moderate risk	×	✓	✓	✓	✓	✓	×	✓
Descatha et al. 2014[23]	High risk	✓	×	×	×	✓	✓	×	✓
Fadel et al. 2019[46]	High risk	×	✓	✓	×	✓	✓	✓	✓
Haines et al. 2017[47]	High risk	×	✓	✓	✓	×	✓	✓	✓
Hanincek et al. 2008[55]	High risk	×	×	✓	×	×	✓	✓	?
Lucas et al. 2013[48]	High risk	×	×	✓	✓	✓	✓	×	×
Mikkelsen et al. 1978[49]	High risk	?	×	×	×	×	×	×	?
Morelli et al. 2017[50]	Moderate risk	✓	×	✓	✓	✓	✓	×	✓
Murinova et al. 2021[51]	High risk	×	✓	✓	?	✓	✓	?	✓
Palmer et al. 2014[52]	High risk	×	✓	✓	×	✓	✓	×	✓
Thomas & Clarke 1992[53]	High risk	×	×	✓	×	×	×	✓	×
Van den Berge et al. 2023[54]	Moderate risk	✓	✓	✓	?	✓	✓	✓	✓

✓ = comply with criteria, × = do not comply with criteria, ? = no information is provided.

Figure 2. Risk of bias summary presented as percentage of the distribution between the 15 included articles for each domain's criteria.



3.4 Association between occupational mechanical exposures and Dupuytren's disease

Measures of association between occupational mechanical exposures and DD reported in the 15 included articles are presented in Appendix 5. Occupational mechanical exposures were divided into four exposure categories: 1) Hand-transmitted vibration, 2) Lifting/carrying loads, 3) Combined mechanical exposures, and 4) Others.

The '*combined mechanical exposure*' group consisted of occupational mechanical exposures that refer to the simultaneous impact of various mechanical exposures that workers may encounter, e.g., forceful exertions, repetitive hand movements, vibrations, and lifting/carrying load.

Among these exposures, 10 studies reported exposure to '*Hand-transmitted vibration*',[23 42 44-48 51-53] four studies reported exposure to '*Lifting/carrying loads*',[23 46 48 52] eight studies reported on exposure to '*Combined mechanical exposures*',[45 47-51 54 55] and two studies reported exposure as '*Others'*.[23 52] The category entitled 'Others' encompasses other mechanical exposures that could not be categorised in the above-mentioned exposure categories. Therefore, the category is not included in the results due to large heterogeneity between measurements, categorisations, and metrics.

Only one study provided a measure of association as a prevalence ratio (PR) instead of an OR.[52] Based on the assumption that the prevalence of a disease is low (<10%, in the exposed and unexposed populations), the PR can approximate an OR.[39] Burke et al[43] was not included in the meta-analysis since they analysed years exposed to vibrations as a continuous variable in the logistic regression. Neither did they provide sufficient information that made it possible for us to calculate an OR between exposed and non-exposed cases and controls.

3.4.1 hand-transmitted vibration

Ten studies reported on the exposure to hand-transmitted vibration and the methodological quality was assessed as moderate risk of bias in two studies[42 45] and as high risk of bias in eight studies.[23 44 46-48 51-53] The exposure definition differed between studies from duration of the use of vibrating tools, years of exposure to vibrations, cumulative exposure, to the average daily use of vibrating tools. The unit of measure was either hours per day, years exposed, or used a dichotomous/categorical approach.

No double-counting data were identified; therefore, ten studies were included in the meta-analysis encompassing ten exposure groups. All except one exposure group were in favour of an association: ORs ranging from 1.0 to 6.2. In the meta-analysis, we found a pooled OR of 2.0 (95% CI 1.5 - 2.7) for being exposed to hand-transmitted vibration, showing a substantial degree of heterogeneity (I^2 = 64.32%) (Figure 3). The funnel plot indicated publication bias (Appendix 6) and Egger's test yielded a statistically significant p-value of 0.014.

Stratifying the meta-analysis based on our risk of bias assessments, the moderate risk of bias studies showed a pooled OR of 4.3 (95% CI 2.3 - 8.3) and the high risk of bias studies showed a pooled OR of 1.6 (95% CI 1.4 - 1.9).

Exposure-response relations were not tested in any of the included studies. Among the ten studies, four studies presented a measure of association containing $\geq$3 exposure groups. The scatter plots are presented in Appendix 7, and all four studies indicated an increase in OR with increasing exposure levels.

Based on the existing literature, evidence of a causal association is likely. Positive associations were found in all except one study (pooled OR of 2.0). However, the association could be explained by chance, bias, confounding (eight out of ten studies were assessed as having a high risk of bias), or publication bias (Egger's test = 0.014), although it might not be a probable explanation. Based upon this, we assessed the degree of evidence of a causal association between hand-transmitted vibration and DD as moderate evidence (appendix 3).

3.4.2 Lifting/carrying loads

Four studies reported on the exposure to lifting/carrying loads and the methodological quality was assessed as high risk of bias in all.[23 46 48 52] The exposure definition differed between studies from years of carrying loads, exposure to manual handling once during a year, to exposure to lifting weights at work. Two studies used years as the unit of measure and three as either categorical or dichotomous variables.

No double-counting data were identified, and all four studies were included in the meta-analysis, encompassing five exposure groups. All except one exposure group were in favour of an association: ORs ranging from 0.9 to 2.2. In the meta-analysis, we found a pooled OR of 1.5 (95% CI 1.1 - 2.0) for being exposed to lifting/carrying loads, showing a considerable degree of heterogeneity (I^2 = 76.73%) (Figure 4). The funnel plot was difficult to interpret due to few studies but did not indicate publication bias (Appendix 6) and Egger's test yielded a non-statistically significant p-value of 0.42.

Exposure-response relations were not tested in any of the included studies. Among the four studies, three presented a measure of association containing $\geq$3 exposure groups. The scatter plots are presented in Appendix 7, and two indicated and increase in OR with increasing exposure levels.

Based on the existing literature, evidence of a causal association is possible. All but one measure of associations was in favour of a positive association. But it is not unlikely that this association can be explained by chance, bias, or confounding (all studies were assessed as having a high risk of bias). Based upon this, we assessed the degree of evidence of a causal association between lifting/carrying loads and DD as limited evidence (appendix 3).

3.4.3 Combined mechanical exposures

Eight studies reported on the exposure to combined mechanical exposures and the methodological quality was assessed as moderate risk of bias in three studies and as high risk of bias in the remaining five studies. The exposure definition differed between studies from exposure to heavy handwork, lifetime work exposure, cumulative manual work, to long-term strenuous manual work. The unit of measure was either dichotomous or categorical (e.g., low/medium/high) approach.

No double-counting data were identified, and all eight studies were included in the meta-analysis, encompassing nine exposure groups. All except one exposure group were in favour of an association: ORs ranging from 1.0 to 18.4. In the meta-analysis, we found a pooled OR of 2.1 (95% CI 1.4 - 3.1) for being exposed to combined mechanical exposures, showing a considerable degree of heterogeneity (I^2 = 97.29%) (Figure 5). The funnel plot indicated publication bias (Appendix 6) and Egger's test yielded a statistically significant p-value of <0.01.

Stratifying the meta-analysis based on our risk of bias assessments, the moderate risk of bias studies showed a pooled OR of 1.1 (95% CI 1.0 - 1.3) and the high risk of bias studies showed a pooled OR of 2.6 (95% CI 1.8 - 3.7).

Exposure-response relations were not tested in any of the included studies. Among the eight studies, four presented a measure of association containing ≥3 exposure groups. The scatter plots are presented in Appendix 7, and all indicated an increase in OR with increasing exposure levels.

Based on the existing literature, evidence of a causal association is possible. All but one measure of association was in favour of a positive association, but only six were significant. It is not unlikely that this association can be explained by chance, bias, confounding (five out of eight studies were assessed as having a high risk of bias), or publication bias (Egger's test <0.01). Based upon, we assessed the degree of evidence of a causal association between combined mechanical exposures and DD as limited evidence (appendix 3).

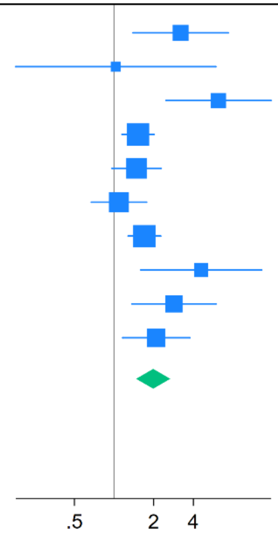
3.4.4 Sex differences

Only two studies have investigated the association between occupational mechanical exposures and DD stratified by sex. Descatha 2014 investigated exposure to lifting/carrying loads utilising two distinct measurements for men (years of exposure) and women (dichotomous approach).[23] Mikkelsen 1978 examined exposure to manual work on each sex, revealing differences in the measure of associations.[49] Notably, women demonstrated a higher odds ratio (OR 18.4) compared to men (OR 2.8), although the odds ratio was subject to a considerably uncertainty. Consequently, no definitive conclusion can be made regarding the existence of sex differences based on the current available evidence.

Figure 3. Forest plot of the association between hand-transmitted vibration and Dupuytren's disease.

Hand-transmitted vibration

Study	Exposure	Exposure group^	Reference group^^	Adjusted for ASSAD + others		OR with 95% CI	Weight (%)
Bovenzi 1994	Lifetime cumulative vibration dose, men	>24 (N=27/110)	Controls(N=9/249)	●●●●○ +1		3.2 [1.4, 7.4]	7.6
Dasgupta 1996	Exposure to vibration, jackhammers, men	Exposed (N=4/62)	Controls (N=2/32)	○○○○○ +0		1.0 [0.2, 5.9]	2.5
Descatha 2012	Use of vibrating tools, men	>2 hours/day (N=11/396)	Never (N=8/1415)	●●○○● +0		6.2 [2.5, 15.5]	6.7
Descatha 2014	Years exposed to vibrating tools, men	>15 years (N=88/693)	No (N=614/7012)	●●●●● +1		1.5 [1.1, 2.0]	16.1
Fadel 2019	Exposure to forarm rotation/vibrating tools, men & women	Exposed (N=47/7864)	Non-exposed (N=51/15833)	○●●●● +0		1.5 [1.0, 2.3]	13.5
Haines 2017	Vibration tool use, men & women	Exposed (N=44/58)	Non-exposed (N=85/122)	○○○○○ +0		1.1 [0.7, 1.8]	12.6
Lucas 2008	Using a vibrating tool at least once during a year, men	Exposed (N=81/660)	Non-exposed (N=131/1746)	○●○○○ +0		1.7 [1.3, 2.3]	16.0
Murinova 2021	Hand-transmitted vibrations, men	Exposed (N=46/147)	Controls (N=9/206)	●●●●● +8		4.6 [1.6, 13.2]	5.6
Palmer 2014	Average daily vibration exposure, men	>2.8 ms (N=14/395)	Never (N=28/2654)	●●●○○ +4		2.8 [1.4, 5.9]	8.7
Thomas & Clarke 1992	Exposure to vibration, men	Claimants (N=62/249)	Controls (N=16/134)	●●○○○ +0		2.1 [1.2, 3.8]	10.8
Overall						2.0 [1.5, 2.7]	



Heterogeneity: $\tau^2 = 0.12$, $I^2 = 64.32\%$, $H^2 = 2.80$

Test of $\theta_i = \theta_j$: $Q(9) = 20.13$, $p = 0.02$

Test of $\theta = 0$: $z = 4.51$, $p = 0.00$

Random-effects REML model

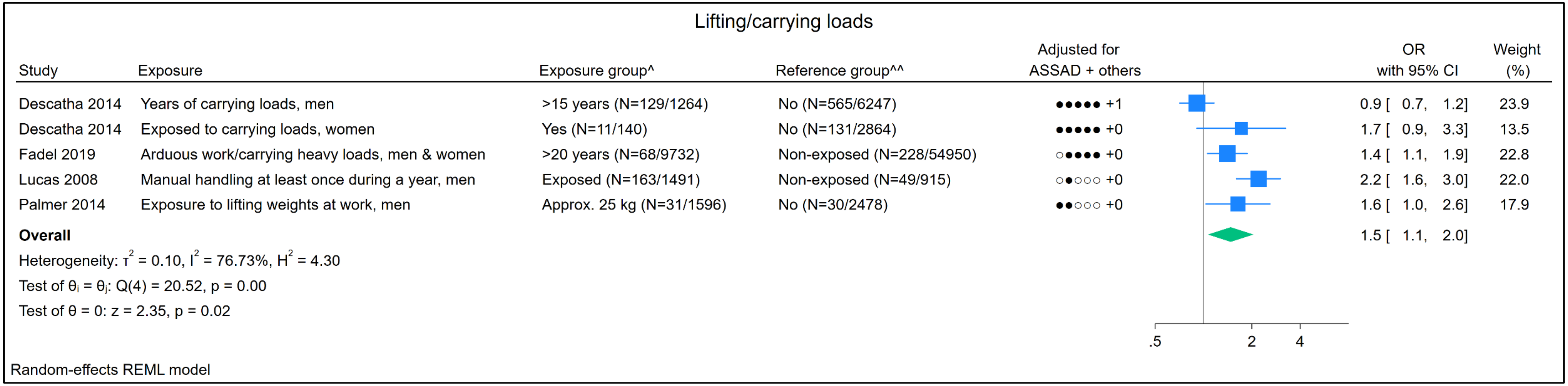
Abbreviations: N=numbers, OR=odds ratio.

^In brackets, number of exposed persons with Dupuytren's disease and number of exposed references.

^^In brackets, number of unexposed men with Dupuytren's disease and number of unexposed references.

Adjusted for ASSAD = age, sex, smoking, alcohol consumption, and diabetes.

Figure 4. Forest plot of the association between lifting/carrying loads and Dupuytren's disease.

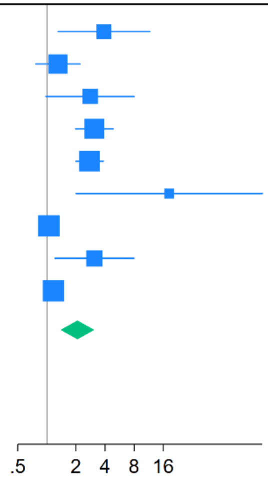


Abbreviations: N=numbers, OR=odds ratio.
^In brackets, number of exposed persons with Dupuytren's disease and number of exposed references.
^^In brackets, number of unexposed men with Dupuytren's disease and number of unexposed references.
Adjusted for ASSAD=age, sex, smoking, alcohol consumption, and diabetes.

Figure 5. Forest plot of the association between combined mechanical exposures and Dupuytren's disease.

Combined mechanical exposures

Study	Exposure	Exposure group^	Reference group^^	Adjusted for ASSAD + others	OR with 95% CI	Weight (%)
Descatha 2012	Exposure to heavy manual work, men	Heavy manual work only (N=5/199)	No exposure (N=10/1518)	●●○○● +0	3.9 [1.3, 11.6]	7.4
Haines 2017	Exposure to heavy handwork, men & women	Exposed (N=99/30)	Non-exposed (N=129/51)	○○○○○ +0	1.3 [0.8, 2.2]	12.7
Hnanicek 2007	Long-term strenuous manual work, men & women	Exposed (N=30/5)	Non-exposed (N=60/28)	●○○○○ +1	2.8 [1.0, 8.0]	7.7
Lucas 2008	Lifetime work exposure, men	High (N=106/643)	Non-exposed (N=33/783)	●●○●● +4	3.1 [2.0, 4.8]	13.6
Mikkelsen 1978	Exposure to manual work, men	Heavy (N=70/477)	Non-exposed (N=96/1805)	○●○○○ +0	2.8 [2.0, 3.8]	14.7
Mikkelsen 1978	Exposure to manual work, women	Heavy (N=1/6)	Non-exposed (N=10/1104)	○●○○○ +0	18.4 [2.0, 168.1]	2.7
Morelli 2017	Heavy manual work for at least 2 years, men & women	Exposed (N=NS)	Non-exposed (N=NS)	●●○○○ +0	1.0 [1.0, 1.1]	16.3
Murinova 2021	Heavy manual work, men	Exposed (N=14/93)	Controls (N=9/206)	●●●●● +8	3.1 [1.2, 7.9]	8.6
Van den Berge 2023	Cumulative manual work, men & women	Exposed (N=114/12198)	Non-exposed (N=382/46242)	●●●●● +7	1.2 [1.1, 1.3]	16.2
Overall					2.1 [1.4, 3.1]	



Heterogeneity: $\tau^2 = 0.26$, $I^2 = 97.29\%$, $H^2 = 36.94$

Test of $\theta_i = \theta_j$: Q(8) = 79.80, p = 0.00

Test of $\theta = 0$: z = 3.55, p = 0.00

Random-effects REML model

Abbreviations: N=numbers, OR=odds ratio.

^In brackets, number of exposed persons with Dupuytren's disease and number of exposed references.

^^In brackets, number of unexposed men with Dupuytren's disease and number of unexposed references.

Adjusted for ASSAD = age, sex, smoking, alcohol consumption, and diabetes.

Table 3 presents an overview of the results of this systematic review and meta-analysis of the association between occupational mechanical exposures and DD.

Table 3. Overview of the pooled ORs, the stratification based on our risk of bias assessment, and the level of evidence based on each included exposure in the meta-analysis.

Mechanical exposures	No. of studies	Pooled OR	Stratified analysis		Publication bias	Level of evidence*
			Moderate risk of bias	High risk of bias		
Hand-transmitted vibration	10	2.0 (95% CI 1.5 - 2.7)	4.3 (95% CI 2.3 - 8.3) (N=2 studies)	1.6 (95% CI 1.4 - 1.9) (N=8 studies)	Indication of publication bias. Egger's test of 0.0014.	Moderate evidence of a causal association.
Lifting/carrying loads	5	1.5 (95% CI 1.1 - 2.0)	Not applicable.	Not applicable.	Indication of publication bias. Egger's test of 0.42.	Limited evidence of a causal association.
Combined mechanical exposures	8	2.1 (95% CI 1.4 - 3.1)	1.1 (95% CI 1.0 - 1.3) (N=3 studies)	2.6 (95% CI 1.8 - 3.7) (N=5 studies)	Indication of publication bias. Egger's test of 0.014.	Limited evidence of a causal association.

* See Appendix 3 for clarification of the assessment.

4. Discussion

4.1 Main results

The results of our systematic review and meta-analysis builds upon 15 included studies. The 15 studies encompassed 11 cross-sectional studies, three case-control studies, and one cohort study published between 1978 and 2023. The risk of bias assessment resulted in five studies assessed as moderate risk of bias and 10 studies assessed as high risk of bias. The meta-analysis showed a pooled OR of 2.0 (95% CI 1.5 - 2.7) of the association between hand-transmitted vibration and DD. A pooled OR of 2.1 (95% CI 1.4 - 3.1) was found of the association between combined mechanical exposures and DD, and finally, a pooled OR of 1.5 (95% CI 1.1 - 2.0) was found of the association between lifting/carrying loads and DD.

In the sensitivity analysis, stratifying the pooled OR based upon the risk of bias assessment, a higher OR was found in studies assessed as "moderate risk of bias" for exposure to vibrations. Conversely, a higher OR was found in studies assessed as "high risk of bias" in the combined mechanical exposures. All studies included in exposure to lifting/carrying loads was assessed as having a "high risk of bias"; therefore, no sensitivity analysis was conducted.

Grading the evidence, we found moderate evidence of a causal association between vibrations and DD. For the remaining two exposure categories, combined mechanical exposures and lifting/carrying loads, we assessed the evidence of a causal association as limited.

4.2 Methodological considerations

The assumptions related to calculating a meta-analysis require homogeneity between exposure measurements, study populations, study designs, etc. Since these methodological variabilities occur in our systematic review, the results should be interpreted with caution, even though we used a random-effects model stating that studies cannot be assumed to estimate the same quantity. In relation to the exposure definition and assessment of the included studies, we observed a large heterogeneity between studies. The exposure definition related to, e.g., vibrations consisted of definitions comprising cumulative measures, years of exposure, daily exposures, and dichotomous approaches. The same methodological variabilities were observed for the combined mechanical exposures and lifting/carrying load. For combined mechanical exposures, only the high exposed vs non-exposed groups were compared but the exposure definitions varied from heavy work, long-term strenuous work, to cumulative manual work. Exposure to lifting/carrying loads contained the same methodological heterogeneities. Consequently, the meta-analysis of this systematic review should be interpreted with caution and was only conducted to visualise the overall effect of each occupational mechanical exposure.

From the data extraction, we chose the measure of association between the highest vs the lowest exposure groups. This approach was chosen to ensure exposure contrast between groups but could have affected our results with an increased risk of type 2 error. Since the highest exposure groups often contains fewer participants, the standard error of a given measure of association might be large, resulting in broader confidence intervals and generally affects the uncertainty in the pooled estimate. Despite this uncertainty, our meta-analysis still yielded significant results for all three occupational mechanical exposure groups.

All exposure assessments included in our systematic review comprised of subjectively measures, such as questionnaires, interviews, or expert ratings, except one study that assessed the exposure using observations. The literature shows that self-reporting can be affected by recall bias and when the exposure covers decades of working history, the likelihood of misclassification increases.[56] In combination with the high proportion of cross-sectional study design, it might be possible that exposure misclassification occurred. In addition, a worker with DD might be prone to categorise their occupation as physically hard/strenuous.[57]

Unfortunately, it was not possible for us to translate the literature written in a foreign language, why the respective studies (as shown in appendix 4) were excluded from our systematic review. This could potentially have affected our results since we identified a total of 12 studies in the process of full-text reading that we were not able to interpret. A few studies have previously been included in other systematic reviews, revealing positive associations.[27 28] Consequently, we can only surmise the effect of not including these measures of association would have on our pooled estimates. Despite this, the aim was to include all literature complying with the stated criteria from our PECOS, no matter the quality, to ensure a thorough synthesis and evaluation.

Recruiting participants seeking medical attention could induce selection problems if people are more likely to be exposed, working in manual occupations. This could potentially contribute to the skewness of the included participants, which provides an over-representation of participants being exposed among cases, hereby creating or enhancing the association. On the contrary, healthier workers might stay longer in exposed occupations, while workers who develop DD will change to a less exposed occupation. One is as likely as the other, especially in cross-sectional studies, why the pooled measure of association can be either attenuated or increased depending on the bias problem.

Using surgery codes for DD or register-based information on DD can contribute to an underestimation of participants with DD since most people with DD do not undergo surgery. But if so, it might be later in life when the disease has progressed to a certain point. Conversely, by using surgery codes or register-based information that reduces the number of cases, the specificity is higher, reducing the bias of misclassification based on the outcome information.

It seems that the included studies are targeting selective populations such as miners, stoneworkers, or claimants, whereas only two studies investigated the association in general populations. Furthermore, heterogeneity was also observed comparing the inclusion of confounding variables and differences in demographic data among exposed and non-exposed groups. For instance, Dasgupta et al[44] and Haines et al[47] showed considerable differences between groups of comparison. In Dasgupta et al, "*drillers*" had a higher proportion of participants that smoked and consumed more alcohol. Haines et al did not match cases with controls and their Table 1 showed differences in the distribution between cases and controls in regards of family members with DD, sex, and diabetes. Therefore, confounding might have affected study results.

4.3 Comparing results

When comparing our findings with previously published systematic reviews, differences occurred in inclusion criteria since we did not include studies using job titles as exposures or studies written in other languages than English or the Nordic languages. Despite these differences, the results show similar patterns. For instance, our results align with previous results presented by Descatha et al,[27] Mathieu et al,[28] Gerger et al, [30] and Nilsson et al.[31] On the contrary, Alser et al[22] assessed the level of evidence as "strong" for exposure to manual work, which we found limited. Discrepancies might occur between exposure categories. Alser et al assessed both exposure to manual work and exposure to vibrations as "history of manual work" and DD, not distinguishing between the two exposures. In fact, we assessed exposure to vibrations as moderate evidence of a causal association and limited evidence of a causal association for the combined mechanical exposures (manual work) taking the risk of bias assessment into account. In addition, Gerger et al[30] assessed the certainty of evidence as low considering exposure to hand-arm vibrations and DD. Despite including both longitudinal studies and cross-sectional studies, their result was based on the synthesis of six studies. In our review, we included 10 studies in exposure to vibration even though we might have similar criteria for inclusion. One discrepancy could be the criteria of an article to use adequate statistical methods. We included all articles, even though; they only provided us with numbers of participants as seen in, e.g., Hnanicek et al (Table 3).[55]

Non-occupational associations

Dupuytren's disease has been associated with other non-occupational factors. In a systematic review published in 2020,[22] Alser and colleagues examined nongenetic factors associated with DD. Using the Oxford Centre for Evidence Based Medicine classification, they assessed the level of evidence of the included studies. Strong evidence of an association was found for advanced age (11 studies), male sex (8 studies), family history of DD (4 studies), diabetes mellitus (37 studies), heavy alcohol drinking (15 studies), and smoking (13 studies). Moderate evidence of an association was found for hyperlipidemia (5 studies), history of hand trauma (6 studies), and having a high BMI (3 studies). All factors were in favour of an increased risk of developing DD except having a high BMI. Of the three studies, two studies showed a potential protective effect of having a high BMI and the last study found a non-significant association between increasing BMI and the development of DD.

Suggestions for future research and practical implications

Dupuytren's disease is a progressive, irreversible disease and, in a research context, studies need to account for time lag between symptoms and onset of the disease. Longitudinal studies are highly warranted to allow for temporality to be interpreted. However, case-control studies would also be considered as a much-needed study design to further investigate the association, keeping the costs lower compared to a cohort study, when the proportion of cases are low. As seen with other chronic illnesses, DD correlates with age. This means that studies would benefit from using statistical methods such as "Risk and rate advancement periods (RAP)" that measures the impact of an exposure to the relation of age, quantifying the time which the rate or risk of a disease is advanced among exposed subjects.[58]

Objective measures of exposures are also highly warranted. Consensus regarding the definition and metric used to estimate the exposure is of the essence to synthesise and compare literature as well as eliminating some of the heterogeneity observed between studies. Furthermore, the conduction of new studies should consider including relevant confounding variables.

5. Conclusion

This reference document was conducted as a systematic review and meta-analysis. Grading the evidence of a causal association, we found moderate evidence of a causal association between vibrations and DD. For the remaining two exposure categories (i.e., combined mechanical exposures and lifting/carrying loads), we assessed the evidence of a causal association as limited. Finally, it was not possible to evaluate sex-differences. Despite various methodological limitations affecting the comparability between the included articles, it is likely that occupational mechanical exposures could influence the development of DD. Consequently, studies of higher quality are warranted.

6. English summary

Introduction

Dupuytren's disease (DD), named after the French surgeon Guillaume Dupuytren, is a progressive, irreversible disease affecting the connective tissue of the palm and fingers. The condition leads to the formation of abnormal collagen deposits in the palmar fascia, an aponeurotic sheet lying deep into the dermis and superficial to the flexor tendons of the hand. The diagnosis is based on clinical symptoms, hand injury history, and medical history. The clinical symptoms are characterised by thickening of the fibrous bands of the palmar fascia, formation of fibromatous nodules, and flexion contractures of the metacarpophalangeal or proximal interphalangeal joints.

It is estimated that 8.2% of the global population is affected by the condition, but the prevalence varies significantly between age groups and geographical locations. Higher prevalence's of Dupuytren's disease typically occurs in elderly population and more often affects elderly men of northern European descent. The mean prevalence of DD based on general populations of Western countries was estimated to 12% at age 55, 21% at age 65, and 29% at age 75 determined from 10 studies.

Genetic factors have been associated with the pathogenesis of DD, but individual and environmental factors are also thought to increase the risk of developing DD, including alcohol, smoking, diabetes, sex, and occupational exposures. Occupational mechanical exposures encompass a range of physical demands that individuals encounter in the work environment such as repetitive movements, forceful exertions, and sustained periods of mechanical loadings. The accumulative effect of occupational mechanical exposures placing stress and strain on the hands tissue has the potential to disrupt repairing processes causing micro trauma, trigger inflammation, promote collagen deposition and the development of contractures. The risk of developing DD among workers exposed to occupational mechanical exposures has been reported in a few reviews, mainly related to vibration exposures.

Since occupational mechanical exposures other than vibrations might be associated with the development of DD, the aim of this systematic review and meta-analysis was to synthesise the existing scientific evidence of the association between occupational mechanical exposures and DD.

Materials and methods

The reference document was conducted as a systematic review and meta-analysis. The systematic literature search was performed the 12th or 13th of April 2023 in National Library of Medicine

(Medline), Excerpta Medica Database (EMBASE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and Web of Science. All articles were independently screened by two authors. We included studies with a population in or above the working-age with current or former employment. The exposure was defined as occupational mechanical exposures, e.g., lifting/carrying loads, repetitive hand movements, hand-arm vibration, or a combination of the aforementioned occupational mechanical exposures. Only outcome defined as Dupuytren's disease (also called Dupuytren's contracture, Morbus Dupuytren, Viking disease, palmar fibromatosis, and Celtic hand), unilateral or bilateral, was included. Finally, we only included quantitative epidemiological studies, i.e., Cohort, case-control, and cross-sectional studies written in English, Danish, Swedish, or Norwegian.

The data extraction was divided into a descriptive table and an analytic table. In the descriptive table, information regarding study characteristics was included. In the analytic table, information regarding confounders, levels of exposure groups, stratifications, and measure of association with its corresponding 95% confidence interval (CI) was included. The data extraction was performed by one author (AJ) and the quality was checked by another author (AD or JHA) to ensure consistency. If any discrepancies occurred, the data extraction was resolved by a third author. To critically appraise the risk of bias of each included article, we used a modified risk of bias tool used in research on chronic diseases. An article could be rated has having a high, moderate, or low risk of bias based on five major domains and three minor domains. The risk of bias assessment was performed independently by two authors (AJ, AD and JHA) and ratings were compared.

To analyse the association between occupational mechanical exposures and DD, we included the measure of association of the highest exposure group vs the lowest exposure group. For each of the occupational mechanical exposure categories, pooled estimates were calculated using random-effects model and the heterogeneity was assessed using I^2-statistics. Publication bias was evaluated from funnel plots and the asymmetry was tested using Egger's test. Finally, sensitivity analyses were conducted by repeating the meta-analyses stratifying studies according to low/moderate vs high risk of bias in order to evaluate the effect of risk of bias in the measure of an association.

The evidence of a causal association between occupational mechanical exposures and DD was assessed according to guidelines provided by The Danish Work Environmental Fund. The quality of evidence could be rated as strong (+++), moderate (++), limited (+), insufficient (0), or evidence suggesting lack of a causal association (-). The assessment was performed independently by two reviewers (AJ and JHA), and further discussed by all authors until consensus.

Results

The literature search yielded 770 articles identified in five scientific databases. After identification of 208 duplicates, 562 articles were screened based on their title and abstract and provided us with 54 articles to full-text reading. After the full-text reading, 15 articles were deemed eligible for inclusion in the systematic review. The epidemiological study design of the included articles consisted of 11 cross-sectional studies, three case-control studies, and one cohort study. In the risk of bias assessment, five studies were assessed as having a moderate risk of bias and 10 studies were assessed as having a high risk of bias. Therefore, no studies were assessed as having a low risk of bias.

Occupational mechanical exposures were divided into four exposure categories: 1) Vibrations, 2) Combined mechanical exposures, 3) Lifting/carrying loads, and 4) Others.

Vibrations: Ten studies were included in the meta-analysis encompassing ten exposure groups. All except one exposure group were in favour of an association: ORs ranging from 1.0 to 6.2. In the meta-analysis, we found a pooled OR of 2.0 (95% CI 1.5 - 2.7) for being exposed to vibrations, showing a substantial degree of heterogeneity (I^2 = 64.32%).

Combined mechanical exposures: Eight studies were included in the meta-analysis, encompassing nine exposure groups. All except one exposure group were in favour of an association: ORs ranging from 1.0 to 18.4. In the meta-analysis, we found a pooled OR of 2.1 (95% CI 1.4 - 3.1) for being exposed to combined occupational mechanical exposures, showing a considerable degree of heterogeneity (I^2 = 97.29%).

Lifting/carrying loads: four studies were included in the meta-analysis, encompassing five exposure groups. All except one exposure group were in favour of an association: ORs ranging from 0.9 to 2.2. In the meta-analysis, we found a pooled OR of 1.5 (95% CI 1.1 - 2.0) for being exposed to combined occupational mechanical exposures, showing a considerable degree of heterogeneity (I^2 = 76.73%).

Conclusion

This reference document was conducted as a systematic review and meta-analysis. Grading the evidence of a causal association, we found moderate evidence of a causal association between vibrations and DD. For the remaining two exposure categories, combined mechanical exposures and lifting/carrying loads, we assessed the evidence of a causal association as limited. A test for exposure-response relations was not conducted in any of the included studies. Scatterplots of studies providing ≥3 exposure groups revealed: Four out of four (4/4) indicated exposure-response relations in the vibrations category and combined exposure category, whereas two out of three (2/3) indicated exposure-response relations in exposure to lifting/carrying loads. Finally, it was not possible to identify exposure thresholds.

7. Danish resume (dansk resume)

Introduktion

Dupuytren's kontraktur (kuskehånd) er opkaldet efter den franske kirurg Guillaume Dupuytren. Det er en kronisk, progressiv sygdom, som rammer senevævet i den berørte hånd. Diagnosen stilles på baggrund af kliniske symptomer, grundig anamnese vedrørende medicinsk- og ulykkeshistorie. De kliniske symptomer viser sig som fortykket senestrøg i håndfladen (palmar fascie) samt strækkedefekt af en eller flere fingre grundet kontrakturer i fingerled. I det tidlige stadie findes kun knudedannelser under huden i håndfladen (prætendinøse bindevæv), men over tid vil en eller flere fingre (hyppigst lille- eller ringfinger) blive trukket ned mod håndfladen grundet kontraktur. Dette efterlader patienten med nedsat funktion som begrænser hverdagsaktiviteter og arbejdsevnen.

Det estimeres, at omtrent 8 % af den globale befolkning vil rammes af kuskehånd, men procenttallet afhænger af aldersgruppe og geografisk lokation. Der ses en højere forekomst blandt den ældre del af befolkningen og hos mænd af nordeuropæisk oprindelse. Blandt generelbefolkningen i de vestlige lande estimeres forekomsten til at være omkring 12 % hos 55-årige, 21 % hos 65-årige samt op til 29 % hos 75-årige.

Der er tidligere fundet sammenhænge mellem genetiske faktorer og kuskehånd, men også individuelle karakteristika samt miljøfaktorer kan øge risikoen for udvikling af kuskehånd. Dette er blandt andet indtag af alkohol, rygning, diabetes, køn og mekaniske belastninger i arbejdet. Mekaniske belastninger i arbejdet omfatter en bred vifte af fysiske belastninger som opstår i arbejdet som f.eks. gentagende bevægelser og kraftudvikling. Den samlede påvirkning over tid kan medføre, at mikrotraumer i håndfladens senestrøg heler langsommere, udløser inflammation og til sidst en kontraktur eller dannelse af knuder i håndfladens senestrøg.

Siden 1996 er der blev udarbejdet flere systematiske reviews på sammenhængen mellem arbejdsrelaterede fysiske belastninger og udvikling af kuskehånd. Overordnet er der blevet kigget på at være eksponeret for vibrationer og en kombination af flere fysiske belastninger på arbejdet (manuelt arbejde). Vibrationer er i denne sammenhæng den mest undersøgte eksponering, men ikke siden 2011 er der blevet udarbejdet en meta-analyse på at være eksponeret for en kombination af flere fysiske belastninger (manuelt arbejde). Arbejdsmarkedets Erhvervssikring og Erhvervssygdomsudvalget har vurderet, at en ny udredning skal udarbejdes i form af et videnskabeligt referencedokument. Formålet med referencedokumentet er at sammenfatte den eksisterende videnskabelige evidens og undersøge sammenhængen mellem arbejdsrelaterede mekaniske belastninger og udvikling af kuskehånd.

Metode og materiale

Referencedokumentet blev udarbejdet som et systematisk review og meta-analyse. Der blev udarbejdet en protokol indsendt til PROSPERO og samtlige retningslinjer til udarbejdelse af et systematisk review givet af PRISMA blev overholdt. Artikler fundet gennem den systematisk litteratursøgning blev vurderet efter vores PECOS (Population, Exposure, Comparison, Outcome, and Study design). Det omfattede alle personer i eller over den arbejdsdygtige alder som var eksponeret for fysiske belastninger i arbejdet såsom vibrationer, løft, repetitive bevægelser mm. og som havde udviklet kuskehånd. Studierne skulle give en sammenligning mellem en eksponeret gruppe mod en ikke/lav eksponeret gruppe med et passende associationsmål eller med mulighed for at udregne en. Vi inkluderede kun epidemiologiske studier (kohorte, case-kontrol og tværsnit) skrevet på engelsk, dansk, svensk eller norsk. Den systematiske litteratursøgning blev anvendt i seks forskellige videnskabelige databaser. Udvælgelse af relevant litteratur blev gjort gennem uafhængige vurdering, først på titel/abstrakt efterfulgt af en fuld gennemlæsning af de resterende artikler.

For alle inkluderede artikler blev relevant information herunder forfatter, studiedesign, udfald, udfaldsvurdering, eksponering, eksponeringsvurdering, confoundere og resultater ekstraheret. Efterfølgende blev artiklernes epidemiologiske kvalitet vurderet ved hjælp af et modificeret kvalitetsværktøj. Kvalitetsværktøjet indeholdt otte epidemiologiske domæner herunder fem "vigtige" domæner og tre "mindre vigtige" domæner. Baseret på de otte domæner blev hver artikels epidemiologiske kvalitet vurderet til at have lav, moderat eller høj risiko for bias.

Der blev foretaget en meta-analyse for at undersøge sammenhængen mellem arbejdsrelaterede mekaniske belastninger og udvikling af kuskehånd som visuelt blev præsenteret i forest plots. Graden af heterogenitet blev vurderet ved hjælp af I^2-statistik som udtrykker graden af forskelligartethed mellem studierne. For at undersøge publikationsbias benyttede vi os af funnel plots og testede for asymmetri via Egger’s test. Sensitivitetsanalyser blev lavet på baggrund af en opdeling på vores risiko for bias og eksponering-respons sammenhænge blev undersøgt via scatter plots.

Evidensgraden for en sammenhæng mellem arbejdsrelaterede belastninger og udvikling ad kuskehånd blev undersøgt via retningslinjer fra Arbejdsmiljøforskningsfonden. Den blev vurderet på forskellige parametre som antal studier, de vægtede estimater, risiko for bias mm. Evidensgraden kunne vurderes som god (+++), nogen (++), begrænset (+), utilstrækkelig (0) eller god evidens for manglende årsagssammenhæng (-).

Resultater

I den systematiske litteratursøgning blev der i alt identificeret 770 artikler, hvoraf 208 var dubletter. Efter screening på titel/abstrakt, 54 artikler blev læst på fuldtekst og til sidst blev 15 artikler inkluderet. Fem studier blev vurderet til at have en moderat risiko for bias, 10 studier vurderet til en høj risiko for bias og ingen studier vurderet til at have en lav risiko for bias.

Vi kategoriserede eksponeringerne i fire mulige kategorier: 1) Vibrationer, 2) Kombinerede eksponeringer, 3) Løftearbejde og 4) Andre eksponeringer.

Vibrationer: Sammenhængen blev undersøgt i 10 studier og vi vurderede, at to studier havde moderat risiko for bias og otte studier en høj risiko for bias. En vægtet OR blev udregnet til 2,0 (95% CI 1,5 til 2,7) som viste en forholdsvis stor heterogenitet blandt studierne (I^2=64,32 %). Funnel plot og Egger's test viste også tegn på publikationsbias. I den stratificerede analyse baseret på vores risiko for bias vurderinger havde studier med moderat risiko for bias en vægtet OR på 4,3 (95 % CI 2,3 til 8,3) og studier med høj risiko for bias en OR på 1,6 (95 % CI 1,4 til 1,9). Derudover blev eksponering-responssammenhænge undersøgt og ingen studier havde lavet et test. Vores scatter plots viste, at blandt fire studier med $\geq$3 eksponeringsgrupper indikerede alle fire en eksponering-responssammenhæng. På baggrund af ovenstående vurderes der at foreligge en moderat grad af evidens for en årsagssammenhæng.

Kombinerede eksponeringer: Sammenhængen blev undersøgt i otte studier og vi vurderede, at tre studier havde moderat risiko for bias og fem studier en høj risiko for bias. En vægtet OR blev udregnet til 2,1 (95% CI 1,4 til 3,1) som viste en høj grad af heterogenitet blandt studierne (I^2=97,29 %). Funnel plot og Egger's test viste også tegn på publikationsbias. I den stratificerede analyse baseret på vores risiko for bias vurderinger havde studier med moderat risiko for bias en vægtet OR på 1,1 (95% CI 1,0 til 1,3) og studier med høj risiko for bias en OR på 2,6 (95% CI 1,8 til 3,7). Derudover blev eksponering-responssammenhænge undersøgt i et enkelt studie. Vores scatter plots viste, at blandt fire studier med $\geq$3 eksponeringsgrupper indikerede alle fire en eksponering-responssammenhæng. På baggrund af ovenstående vurderes der at foreligge en begrænset grad af evidens for en årsagssammenhæng.

Løftearbejde: Sammenhængen blev undersøgt i fire studier og vi vurderede, at alle studier havde en høj risiko for bias. En vægtet OR blev udregnet til 1,5 (95% CI 1,1 til 2,0) som viste en forholdsvis stor heterogenitet blandt studierne (I^2=76,73 %). Funnel plot og Egger's test viste ikke tegn på publikationsbias, men var svær at vurdere grundet de få studier. Eksponering-responssammenhænge blev ikke undersøgt i nogen studier. Vores scatter plots viste, at blandt tre studier med $\geq$3 eksponeringsgrupper indikerede to en eksponering-responssammenhæng. På baggrund af ovenstående vurderes der at foreligge en begrænset grad af evidens for en årsagssammenhæng.

Resultaterne fra meta-analyserne viste store epidemiologiske forskelle mellem studierne på baggrund af definition og vurdering af eksponeringerne, justeringer foretaget i analyserne samt de inkluderede stikprøver. Det kan på denne baggrund være vanskeligt at sammenligne studierne og deres resultater, hvorfor resultaterne skal tolkes forsigtigt.

Konklusion

I dette referencedokument udarbejdet som et systematisk review og meta-analyse har vi vurderet, at der ved den nuværende epidemiologiske evidens er moderat evidens for en årsagssammenhæng mellem vibrationer og udvikling af kuskehånd. Derudover vurderer vi, at der er begrænset evidens for en årsagssammenhæng mellem både kombineret eksponeringer og løftearbejde og udviklingen af kuskehånd. Slutteligt var det ikke muligt at identificere sikre tærskelværdier.

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51. Murinova L, Perecinsky S, Jancova A, et al. Is Dupuytren's disease an occupational illness? *Occup Med (Lond)* 2021;71(1):28-33. doi: 10.1093/occmed/kqaa211
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Appendix

Occupational mechanical exposures and Dupuytren's disease: a reference document

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Appendix 1. Literature search

Aggregated search string:

("dupuytren*"[Text Word] OR "palmar fibromatos*"[Text Word] OR "dupuytren contracture"[MeSH Terms] OR palmar fascia*[tw]) AND ("work*"[Text Word] OR "occupation*"[Text Word] OR "job"[Text Word] OR "occupational exposure"[MeSH Terms] OR "vibration"[MeSH Terms] OR "weight bearing"[MeSH Terms] OR "lifting"[MeSH Terms] OR "axial loading*"[Text Word] OR "Bending"[Text Word] OR "Carrying"[Text Word] OR "heavy lifting"[Text Word] OR "load bearing"[Text Word] OR "Loadbearing"[Text Word] OR "physically demanding"[Text Word] OR "Pull"[Text Word] OR "Pulling"[Text Word] OR "repetitive work"[Text Word] OR "strain"[Text Word] OR occupations[mh] OR Work[mh])

Appendix 2. Risk of bias assessment tool

Cohort Study	**Yes**	**No**	**Unclear**
Major domain 1 – study design and selection			
Was the cohort recruited in an acceptable way? Consider the following: ● Is it representative of a defined population and clearly specified? ● Are groups comparable in all respects other than the factor under investigation? ● Was everybody included who should have been?			
Was the follow-up of subjects acceptable? Consider the following: ● Conventionally, a 20% drop out rate is acceptable, but observational studies conducted over longer periods, a higher drop-out rate is to be expected. ● Were losses to follow-up taken into account in the analysis (sensitivity analysis, described etc.)?			
Major domain 2 – Exposure			
Was the exposure accurately measured to minimise bias? Consider the following: ● Is the exposure clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable? ● Were all the subjects classified into exposure groups using the same procedure?			
Major domain 3 – Outcome			
Was the outcome accurately measured to minimise bias? Consider the following: ● Is the outcome clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable? ● Were the measurement methods similar in the different groups? ● If blinding is not possible, is there some recognition that knowledge of exposure status could influence the assessment of the outcome?			
Major domain 4 – Enrolment			
Was the outcome taken into account at enrolment? Consider the following: ● Some participants might have the outcome at the time of enrolment. Is it assessed at baseline in the analysis?			
Major domain 5 – Analysis method			
Was the analysis method adequate? Consider the following: ● Are the main potential confounders identified and taken into account in the analysis? ● Were adequate statistical models used to reduce bias?			
Minor domain 1 – Funding			
Was the source of funding provided? Consider the following: ● Was the study affected by sponsors? ● Did sponsoring organization participate in the analysis?			
Minor domain 2 – Chronology			
Could chronology be established? Consider the following: ● Was the timeframe sufficient to see an association between the exposure and outcome? ● Was the follow-up long enough for the outcome to occur?			
Minor domain 3 – Conflict of interest			
Was the study without any conflict of interest? Consider the following: ● Was the study affected by the authors affiliations or interests?			

Cross-sectional studies	Yes	No	Unclear
Major domain 1 – study design and selection			
Were the subjects recruited in an acceptable way? Consider the following: ● Are subjects' representative of a population, clearly defined and differentiated from controls? ● Was the method of selection of the subjects clearly described? ● Could the way the sample was obtained introduce bias?			
Is the participation rate satisfactory? Consider the following: ● Was the sample size based on pre-study considerations of statistical power? ● Was a satisfactory response rate achieved or was the sample size justified?			
Major domain 2 – Exposure			
Was the exposure accurately measured to minimise bias? Consider the following: ● Is the exposure clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable?			
Major domain 3 – Outcome			
Was the outcome accurately measured to minimise bias? Consider the following: ● Is the outcome clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable?			
Major domain 4 – Non-participants			
Is comparison made between participants and non-participants? Consider the following: ● Is similarities or differences established?			
Major domain 5 – Analysis method			
Was the analysis method adequate? Consider the following: ● Are the main potential confounders identified and taken into account in the analysis? ● Were adequate statistical models used to reduce bias?			
Minor domain 1 – Funding			
Was the source of funding provided? Consider the following: ● Was the study affected by sponsors? ● Did sponsoring organization participate in the analysis?			
Minor domain 2 – Chronology			
Could chronology be established? Consider the following: ● Was the timeframe sufficient to see an association between the exposure and outcome? ● Was the follow-up long enough for the outcome to occur?			
Minor domain 3 – Conflict of interest			
Was the study without any conflict of interest? Consider the following:			

● Was the study affected by the authors affiliations or interests?			

Case-Control Study	**Yes**	**No**	**Unclear**
Major domain 1 – study design and selection			
Were the cases recruited in an acceptable way? Consider the following: ● Are the cases representative of a population, clearly defined and differentiated from controls? ● Was there an established reliable system for selecting all the cases? ● Were inclusion and exclusion criteria explicit and applied similarly to all eligible cases?			
Were the controls selected in an acceptable way? Consider the following: ● Are the controls representative of a population and clearly defined? ● Are the same inclusion and exclusion criteria for cases used to select controls (equally applied) and matched appropriately? ● Is it clearly established that controls are non-cases?			
Is the participation rate satisfactory? Consider the following: ● Are there large differences between the two groups? ● Is the participation rate low?			
Major domain 2 – Exposure			
Was the exposure accurately measured to minimise bias? Consider the following: ● Is the exposure clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable?			
Major domain 3 – Outcome			
Was the outcome accurately measured to minimise bias? Consider the following: ● Is the outcome clearly defined? ● Do measurements truly reflect what it is supposed to measure (have they been validated?). ● Is the method of assessment reliable?			
Major domain 4 – Non-participants			
Is comparison made between participants and non-participants? Consider the following: ● Is similarities or differences established?			
Major domain 5 – Analysis method			
Was the analysis method adequate? Consider the following: ● Are the main potential confounders identified and taken into account in the analysis? ● Were adequate statistical models used to reduce bias?			
Minor domain 1 – Funding			
Was the source of funding provided? Consider the following: ● Was the study affected by sponsors? ● Did sponsoring organization participate in the analysis?			
Minor domain 2 – Chronology			
Could chronology be established? Consider the following: ● Was the timeframe sufficient to see an association between the exposure and outcome?			
Minor domain 3 – Conflict of interest			
Was the study without any conflict of interest? Consider the following: ● Was the study affected by the authors affiliations or interests?			

Appendix 3. Evidence of an association

Danish Labour Market Insurance and Occupational Diseases Committee

Degree of evidence for a causal association between exposure to a specific risk factor and a specific outcome.

The following categories are applied:

+++	Strong evidence of a causal association
++	Moderate evidence of a causal association
+	Limited evidence of a causal association
0	Insufficient evidence of a causal association
-	Evidence suggesting lack of a causal association

Description of categories:

Strong evidence of a causal association (+++): A causal association is very likely. A positive relation between exposure to a risk factor and outcome has been observed in several epidemiological studies. It can be excluded with a reasonable degree of certainty that this association can be explained by chance, bias or confounding.

Moderate evidence of a causal association (++): A causal association is likely. A positive relation between exposure to a risk factor and outcome has been observed in several epidemiological studies. It cannot be excluded with a reasonable degree of certainty that this association can be explained by chance, bias or confounding, although this is not a very probable explanation.

Limited evidence of a causal association (+): A causal association is possible. A positive relation between exposure to a risk factor and outcome has been observed in several epidemiological studies. It is not unlikely that this association can be explained by chance, bias or confounding.

*Insufficient evidence of a causal association (0): A*vailable studies are of insufficient quality, consistency, or statistical weight to allow a conclusion on the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-): Several studies of sufficient quality, consistency and statistical weight suggest that the specific risk factor is not causally related to the specific outcome.

Comments: The classification does not include a category for which a causal association is considered to be established without any doubt. The key criterion is the epidemiological evidence. The probability that chance, bias and confounding can explain observed associations are criteria that includes criteria such as consistency, number of ‘high quality’ studies, types of design etc. Biological plausibility and contributory information can support the evidence of a causal association.

Appendix 4. Excluded articles

Table S1. Excluded articles based on the full-text reading.

	References	**Reason for exclusion**
1	Agustoni CB, Salaberry JF. [Dupuytren's disease as an occupational disease]. Sem Med. 1961;118:404-6.	Foreign language.
2	Bennett B. Dupuytren's contracture in manual workers. British Journal of Industrial Medicine. 1982;39(1):98-100.	Wrong exposure.
3	Bergenudd H, Lindgarde F, Nilsson BE. Prevalence of dupuytren's contracture and its correlation with degenerative changes of the hands and feet and with criteria of general health. Journal of Hand Surgery. 1993;18 B(2):254-7.	No measure of association.
4	Brenner P, Krause-Bergmann A, Van VH. [Dupuytren contracture in North Germany. Epidemiological study of 500 cases]. Unfallchirurg. 2001;104(4):303-11.	Foreign language.
5	Broekstra DC, van den Heuvel ER, Lanting R, Harder T, Smits I, Werker PMN. Dupuytren disease is highly prevalent in male field hockey players aged over 60 years. BRITISH JOURNAL OF SPORTS MEDICINE. 2018;52(20):1327-+.	Wrong exposure.
6	Chanut, J. C. Dupuytren's disease. Retraction of the palmar aponeurosis. A series of 378 cases observed in a large plant. Rev Rhum Mal Osteoartic Jan-Feb 1964;31():24-8	Foreign language.
7	Clarke D, Thomas PR. Vibration white finger and dupuytrens contracture - are they related - reply. Occupational medicine-oxford. 1993;43(2):108-.	Other reasons (e.g., abstracts, books etc.).
8	Cocco PL, Frau P, Rapallo M, Casula D. [Occupational exposure to vibration and Dupuytren's disease: a case-controlled study]. Med Lav. 1987;78(5):386-92.	Foreign language.
9	de la Caffinière JY, Wagner R, Etscheid J, Metzger F. [Manual labor and Dupuytren disease. The results of a computerized survey in the field of iron metallurgy]. Ann Chir Main. 1983;2(1):66-72.	Foreign language.
10	Degreef I, Steeno P, De Smet L. A survey of clinical manifestations and risk factors in women with Dupuytren's disease. Acta Orthopaedica Belgica. 2008;74(4):456-60.	Wrong study design.
11	Descatha A, Bodin J, Ha C, Goubault P, Lebreton M, Chastang JF, et al. Heavy manual work, exposure to vibration and Dupuytren's disease? Results of a surveillance program for musculoskeletal disorders. Occupational and Environmental Medicine. 2011((Descatha, Leclerc, Goldberg) Universite de Versailles St-Quentin, UMRS 1018, Centre for Research in Epidemiology and Population Health, Population-Based Epidemiological Cohorts Research Platform, Villejuif, France(Descatha, Chastang, Leclerc, Goldberg) I).	Other reasons (e.g., abstracts, books etc.).
12	Descatha A, Carton M, Mediouni Z, Dumontier C, Roquelaure Y, Goldberg M, et al. Association between work exposure, alcohol	Other reasons (e.g., abstracts, books etc.).

	intake, smoking and Dupuytren's disease in a large cohort study (Gazel). Occupational and Environmental Medicine. 2014;71(SUPPL. 1):A65.	
13	Descatha A, Raju K. Dupuytrent's disease and occupation: still a debate? Br J Hosp Med (Lond). 2011;72(11):655.	Other reasons (e.g., abstracts, books etc.).
14	Fioravanti A, Cocco R, Francioni C, Innocenti A, Megale F, Priolo F, et al. [A syndrome caused by separating rags in textile industry: a new clinical entity?]. Minerva Med. 1995;86(11):467-4.	Foreign language.
15	Grobe JW. [Dupuytren contracture in Mosel wine dressers with arsenic-induced aftereffect damage]. Derm Beruf Umwelt. 1982;30(6):196-8.	Foreign language.
16	Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A, Jonsson T. Epidemiology of Dupuytren's disease: Clinical, serological, and social assessment. The Reykjavik Study. Journal of Clinical Epidemiology. 2000;53(3):291-6.	Wrong exposure.
17	Hacquebord JH, Chiu VY, Harness NG. The Risk of Dupuytren Diagnosis in Obese Individuals. J Hand Surg Am. 2017;42(3):149-55.	Wrong exposure.
18	Hampl K. [Dupuytren's contracture in engine drivers]. Prac Lek. 1960;12:358-60.	Foreign language.
19	Hueston JT. Dupuytren's contracture and occupation. The Journal of hand surgery. 1987;12(5 Pt 1):657-8.	Other reasons (e.g., abstracts, books etc.).
20	Hutchinson J. Dupuytren's contraction of the palmar fascia - Dupuytrens life and works. LANCET. 1917;1:285-90.	Other reasons (e.g., abstracts, books etc.).
21	Karbowiak M, Holme T, Khan K, Mohan A. Dupuytren's disease. The BMJ. 2021;373((Karbowiak) Royal Surrey County Hospital, Egerton Road, Guildford GU2 7XX, United Kingdom(Holme) Epsom Hospital, Epsom KT18 7EG, United Kingdom(Khan) Stovell House Surgery, Croydon CR0 6AH, United Kingdom(Mohan) Croydon Health Services NHS Trust, Croydon):n1308.	Other reasons (e.g., abstracts, books etc.).
22	Khan AA, Rider OJ, Jayadev CU, Heras-Palou C, Giele H, Goldacre M. The role of manual occupation in the aetiology of Dupuytren's disease in men in England and Wales. J Hand Surg Br. 2004;29(1):12-4.	No measure of association.
23	Loos B.; Puschkin V.; Horch R.E. 50 Years experience with Dupuytren's contracture in the Erlangen University Hospital - A retrospective analysis of 2919 operated hands from 1956 to 2006. BMC Musculoskeletal Disorders / 2007;8.	Wrong exposure.
24	Lorin J. [Frequency of Dupuytren's contracture in manual workers; medico-social aspects]. Arch Mal Prof. 1953;14(1):71-2.	Foreign language.
25	Lurati AR. Dupuytren's Contracture: Work-Related Disorder? WORKPLACE HEALTH & SAFETY. 2017;65(3):96-9.	Wrong study design.

26	Marx J, Schunk W. [The role of occupational and dispositional factors in the development of Dupuytren contracture]. Beitr Orthop Traumatol. 1982;29(9):477-83.	Foreign language.
27	Mikusev IE. [Dupuytren's contracture and occupation]. Ortop Travmatol Protez. 1985(7):42-3.	Foreign language.
28	Palmer KT, D'Angelo S, Syddall H, Griffin MJ, Cooper C, Coggon D. Occupational exposure to hand-transmitted vibration and risk of Dupuytren's contracture. Occupational and Environmental Medicine. 2014;71(SUPPL. 1):A7.	Other reasons (e.g., abstracts, books etc.).
29	Palmer KT, D'Angelo S, Syddall H, Griffin MJ, Cooper C, Coggon D. 0068Occupational exposure to hand-transmitted vibration and risk of Dupuytren's contracture. Occupational & Environmental Medicine.71:A7-A.	Other reasons (e.g., abstracts, books etc.).
30	Rafter D, Kenny R, Gilmore M, Walsh CH. Dupuytren's contracture--a survey of a hospital population. Ir Med J. 1980;73(6):227-8.	Wrong exposure.
31	Roberts FP. VIBRATION WHITE LINGER AND DUPUYTRENS CONTRACTURE. OCCUPATIONAL MEDICINE-OXFORD. 1994;44(1):50-.	Other reasons (e.g., abstracts, books etc.).
32	Roberts FP. A vibration injury - dupuytrens contracture. Journal of the society of occupational medicine. 1981;31(4):148-50.	Wrong study design.
33	Sasaki N, Uesato R, Yamauchi T, Ishibashi Y, Nakaji S. Epidemiology of Dupuytren's Disease in Japanese General Population. Journal of hand surgery Asian-Pacific volume. 2021;26(2):229-34.	Wrong exposure.
34	Stirling PHC, Jenkins PJ, McEachan JE. Previous vibration exposure in patients undergoing surgical treatment of Dupuytren's contracture. The Journal of hand surgery, European volume. 2020;45(5):525-7.	Wrong study design.
35	Stirling PHC, Ng N, Jenkins PJ, Clement ND, Duckworth AD, McEachan JE. Hand-arm vibration and outcomes of surgery for Dupuytren's contracture. Occupational medicine (Oxford, England). 2021;71(4-5):219-22.	Wrong outcome.
36	Tajika T, Kobayashi T, Kaneko T, Tsunoda D, Tsunoda K, Sutou T, et al. Epidemiological study for personal risk factors and quality of life related to Dupuytren's disease in a mountain village of Japan. Journal of Orthopaedic Science. 2014;19(1):64-70.	Wrong exposure.
37	Vasiliadis AV, Charitoudis G, Giotis D, Paschos NK, Malahias MA, Drosos G. Hand disorders demographics in rural areas: A 15-year analysis of demographic characteristics overtime in a stable population. ACTA ORTHOPAEDICA ET TRAUMATOLOGICA TURCICA. 2020;54(6):604-8.	Wrong exposure.
38	Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. Arthritis & rheumatism-arthritis care	Wrong outcome.

	& research. 2004;51(4):642-51.	
39	Zakharov AV. [Dupuytren's contracture in vibration disease]. Vrach Delo. 1967;8:113-5.	Foreign language.

Appendix 5. Measure of association

Table S2. Measure of association of all 15 included studies.

				Men		Women		All	
Author	**Exposure**	**Confounders**	**Categories of exposure**	**Measure of association**	**95% CI**	**Measure of association**	**95% CI**	**Measure of association**	**95% CI**
Vibrations									
Bovenzi 1994	Life-time cumulative doses of vibration (controls vs vibration groups) calculated by the frequency weighted acceleration measured on the vibrating tools, the individually estimated daily exposure, the number of working days in a year, and the number of years during which the tool was used.	Age, smoking, alcohol consumption, and upper limb injuries.	- Controls - <19.5 - 19.5 - 21.5 - 21.5 - 24 - >24	1.00 OR 1.93 OR 2.25 OR 2.57 OR 3.20 OR	- 0.64 - 5.84 0.88 - 5.72 1.04 - 6.36 1.39 - 7.73	- - - - -	- - - - -	- - - - -	- - - - -
	Distribution of Dupuytren's contracture among workers exposed to hand transmitted vibrations (stone workers) vs controls (manual polishers and machine operators)	Age, smoking, alcohol consumption, and upper limb injuries.	- Stone workers	2.60 OR	1.24 - 5.49	-	-	-	-
Burke 2007	The odds ratio reflects the number of years exposed to vibrating tools used as a continuous variable (OR associated with an increase of one unit)	Age, diabetes, smoking, and alcohol consumption.	- 1 year exposure	1.002 OR	0.99 - 1.00	-	-	-	-
Dasgupta 1996	Exposure to vibration when operating a jackhammer at work. OR calculated on the basis of the distribution between cases and controls (jackhammers vs blasters): - Jackhammers, n=4/62 - Blasters, n=2/32 (1 case was excluded)	None.	- Non-exposed - Exposed	1.00 OR 1.03 OR	- 0.18 - 5.94	- -	- -	- -	- -
Descatha	Use of vibrating tools was classified as	Age and diabetes.	- Never	1.0 OR	-	-	-	-	-

2012	never, uncommonly (<2 hours/day), frequently or all the time (≥2 hours/day).		- <2 hours/day - >2 hours/day	4.8 OR 6.2 OR	1.7 - 13.5 2.5 - 15.7	- -	- -	- -	- -
	Manual work + vibration exposure was divided into 1) no exposure to vibration and no heavy manual work, 2) no exposure to vibration but exposure to heavy manual work, and 3) exposure to vibration.	Age and diabetes.	- No exposure - Heavy work - Vibration exp.	1.0 OR 3.9 OR 5.1 OR	- 1.3 - 11.5 2.1 - 12.2	- - -	- - -	- - -	- - -
	Use of hand tools (any hand tools including vibrating tools) was classified as never, uncommonly (<2 hours/day), frequently or all the time (≥2 hours/day).	Age and diabetes.	- Never - <2 hours/day - ≥2 hours/day	1.0 OR 2.5 OR 7.7 OR	- 0.3 - 17.8 1.8 - 32.9	- - -	- - -	- - -	- - -
Descatha 2014	Years exposed to manipulating vibrating tools in working life (assessed in 2007).	Men: Age, diabetes, smoking, alcohol consumption, and carrying loads.	- No - 1-15 years - >15 years	1.00 OR 1.25 OR 1.52 OR	- 0.95 – 1.65 1.15 – 2.02	- - -	- - -	- - -	- - -
	Exposed to manipulating vibrating tools (assessed in 1989).	None.	- No - Yes	1.00 OR 1.34 OR	- 1.05 – 1.71	1.00 OR 1.53 OR	- 0.20 – 11.67	- -	- -
	Exposed to manipulating vibrating tools (assessed in 2007).	Women: Age, diabetes, smoking, and alcohol consumption.	- No - Yes	- -	- -	1.00 OR 17.17 OR	- 2.35 – 125.62	- -	- -
Fadel 2019	Exposure to forearm rotation and usage of vibrating tools was evaluated using a JEM rating the participant's exposure from 0 (never or almost never) to 3 (almost always) based on work history. Participants were divided in two groups: not exposed (score =0) and exposed (score >0).	Sex, smoking, alcohol consumption, and diabetes.	- Not exposed - Exposed Stratified by age: - Not exposed - <60 years - ≥60 years	- - - - -	- - - - -	- - - - -	- - - - -	1.00 OR 1.48 OR 1.00 OR 2.08 OR 1.20 OR	- - - - -
Haines 2017	Exposure to vibrating power tool was measured as censored hour intensity scaled by 20,000 in paid work for both	Age, sex, handedness family history, diabetes, CAGE score, alcohol	- Vibrating tools	-	-	-	-	0.982 OR	0.94 - 1.02

	hands combined (hours divided by 10,000 to represent a typical 10 work years of 40 hours per week and 50 weeks a year.	consumption, and smoking.							
	OR calculated for each exposure based upon the distribution of cases and controls in the article. Numbers provided from Table 1: - Vibrating tool use (VT) (cases, n=44/85; controls, n=58/122)	None.	- VT	-	-	-	-	1.09 OR	0.67 - 1.76
Lucas 2013	Using a tool with handle at least once during a working year.	None.	- No - Yes	1.0 OR 2.5 OR	- 1.8 - 3.5	- -	- -	- -	- -
	Using a vibrating tool at least once during a working year.	None.	- No - Yes	1.0 OR 1.7 OR	- 1.3 - 2.3	- -	- -	- -	- -
Murinova 2021	Daily exposure to hand-transmitted vibrations	Age, heavy manual work, alcohol consumption, smoking, diabetes, arterial hypertension, ischaemic heart disease, hypercholesterolemia, hypertriglyceridemia, hepatopathy, goitre arthritis, and epilepsy.	- No - Yes	1.00 OR 4.59 OR	- 1.57 - 12.99	- -	- -	- -	- -
Palmer 2021	Average personal daily vibration exposures for the past week were estimated with cut-off point at 2.8 ms^{-2} root mean squared velocity defining higher levels of exposure.	Age groups, social class, smoking, lifting weights, digging/shovelling, and use of keyboard.	- Never - Ever, not in past week - Past week <=2.8 ms^{-2} - Past week >2.8 ms^{-2}	1.00 PR 1.23 PR 1.51 PR 2.85 PR	- 0.58 - 2.62 0.82 - 2.79 1.37 - 5.97	- - - -	- - - -	- - - -	- - - -
	Exposure to hand-transmitted vibrations in previous paid jobs were coded by a panel of vibration	Age groups, social class, smoking, lifting weights,	- Never - Ever	1.00 PR 1.53 PR	- 0.93 - 2.51	- -	- -	- -	- -

	specialists to classify subjects' lifetime exposure (ever vs never) to relevant occupational tools.	digging/shovelling, and use of keyboard.							
Thomas and Clarke 1992	Years exposed to vibrating tools among claimants. OR calculated on the basis of numbers provided in table 6. The reference group comprised claimants with <10 years' exposure to vibrating tools.	None.	- <10 years - 10-19 years - 20-29 years - +30 years	1.00 OR 3.62 OR 3.83 OR 3.85 OR	- 0.46 - 28.6 0.49 - 30.0 0.50 - 29.6	- - - -	- - - -	- - - -	- - - -
Combined mechanical exposures									
Descatha 2012	The Borg Rating of Perceived Exertion scale was used and classified according to the distribution of answers (<12, 12-14, ≥15).	Age and diabetes.	- <12 - 12-14 - ≥15	1.0 OR 2.6 OR 4.0 OR	- 1.02 – 10.2 1.7 – 16.6	- - -	- - -	- - -	- - -
Haines 2017	Repetitive handwork was measured as censored hour intensity scaled by 20,000 in paid work for both hands combined (hours divided by 10,000 to represent a typical 10 work years of 40 hours per week and 50 weeks a year.	Age, sex, handedness family history, diabetes, CAGE score, alcohol consumption, and smoking.	- Rep. handwork	-	-	-	-	1.016 OR	1.0 - 1.03
	Heavy handwork was measured as censored hour intensity scaled by 20,000 in paid work for both hands combined (hours divided by 10,000 to represent a typical 10 work years of 40 hours per week and 50 weeks a year.	Age, sex, handedness family history, diabetes, CAGE score, alcohol consumption, and smoking.	- Heavy handwork	-	-	-	-	0.99 OR	0.97 - 1.00
	OR calculated for each exposure based upon the distribution of cases and controls in the article. Numbers provided from Table 1: - Heavy handwork (HHW) (cases, n=99/30; controls, n=129/51) - Repetitive handwork RHW) (cases, n=112/17; controls, n=162/18)	None.	- HHW - RHW	- -	- -	- -	- -	1.30 OR 0.73 OR	0.77 - 2.20 0.36 - 1.48

Lucas 2013	Lifetime work exposure (for exposure to tool with handle, vibrating tools, manual handling, and repairing equipment) was assessed as an estimate of average annual frequency multiplied by the number of years worked. The annual frequency was 0.5 for less than a month, 3 for one to six months, and 8 for six to twelve months. The score was then categorised into low, medium, and high exposure.	Age, manual hobbies, family history of DD, diabetes, epilepsy, history of hand trauma, and alcohol consumption.	- Low - Medium - High	1.0 OR 2.2 OR 3.1 OR	- 1.39 - 3.45 1.99 - 4.84	- - -	- - -	- - -	- - -
Mikkelsen 1978	OR was calculated on the basis of the distribution of participants provided in table 1: - Men (Heavy=70/477; Medium=262/2304; Light=218/2285; Non manual work=96/1805). - Women (Heavy=1/6; Medium=223/2304; Light=20/706; Non manual work=10/1104).	None.	- Non man. work - Heavy man. work - Medium - Light	1.00 OR 2.76 OR 2.14 OR 1.79 OR	- 2.00 - 3.82 1.68 - 2.72 1.40 - 2.30	1.00 OR 18.4 OR 10.7 OR 3.13 OR	- 2.0 - 167 5.65 - 20 1.46 - 6.72	- - - -	- - - -
Morelli 2017	Daily heavy manual work	Matched on age and sex.	- Daily heavy work	-	-	-	-	7.36 OR	1.5 - 36.5
	Heavy manual work (years) = past or present daily heavy manual workers for at least 2 years.	Matched on age and sex.	- Heavy work (years)	-	-	-	-	1.05 OR	1.01 - 1.09
Murinova 2021	Heavy manual work included lifting, lowering, pulling, pushing, or carrying a load.	Age, hand-transmitted vibrations, alcohol consumption, smoking, diabetes, arterial hypertension, ischaemic heart disease, hypercholesterolemia, hypertriglyceridemia, hepatopathy, goitre arthritis, and epilepsy.	- No - Yes	1.00 OR 3.10 OR	- 1.21 - 7.91	- -	- -	- -	- -

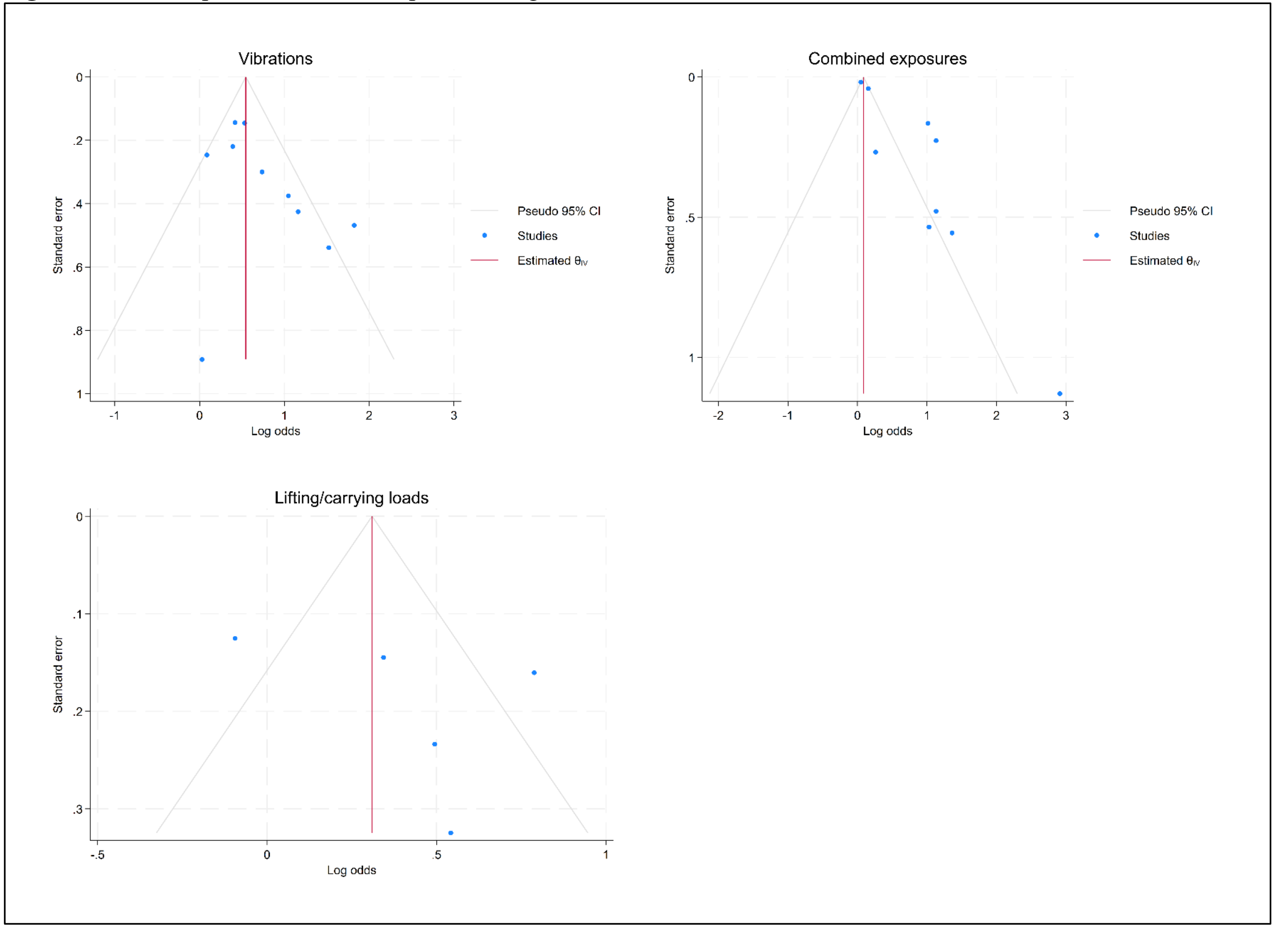
Van den Berge 2023	Exposure to manual work was calculated matching participants on current job: usually + always (exposed) vs rarely + sometimes (unexposed) based on propensity score.	Grouped by propensity score on the following covariates: age, sex, diabetes, hypertension, respiratory disease, smoking, alcohol consumption, BMI, LDL, HDL, triglyceride levels, and TDI	- Unexposed - Exposed	1.00 OR 1.29 OR	- 1.12 - 1.49	- -	- -	- -	- -
	Cumulative manual work was categorised into five groups separated by increments of 750 (<750, 750-1499, 1500-2249, 2250-3000, >3000) standardised O*NET-score multiplied by number of years.	Grouped by propensity score on the following covariates: age, sex, diabetes, hypertension, respiratory disease, smoking, alcohol consumption, BMI, LDL, HDL, triglyceride levels, and TDI.	- Increments of 750	1.17 OR	1.08 - 1.27	-	-	-	-
Lifting/carrying loads									
Descatha 2014	Years exposed to carrying loads in working life (assessed in 2007).	Men: Age, diabetes, smoking, alcohol consumption, and vibrating tools.	- No - 1-15 years - >15 years	1.00 OR 0.95 OR 0.91 OR	- 0.74 – 1.22 0.71 – 1.16	- - -	- - -	- - -	- - -
	Carrying loads (assessed in 1989)	None.	- No - Yes	1.00 OR 1.10 OR	- 0.88 – 1.36	1.00 OR 1.15 OR	- 0.53 – 2.51	- -	- -
	Carrying loads (assessed in 2007)	None.	- No - Yes	- -	- -	1.00 OR 1.72 OR	- 0.91 – 3.25	- -	- -
Fadel 2019	Lifetime exposure to arduous work or carrying heavy loads was grouped based on years of exposure.	Sex, smoking, alcohol consumption, and diabetes.	- No exposure - >0 to <10 years - ≥10 to <20 years - ≥20 years Stratified by age <60 years: - No exposure	- - - - -	- - - - -	- - - - -	- - - - -	1.00 OR 0.88 OR 1.43 OR 1.41 OR 1.00 OR	- 0.56 - 1.40 0.93 - 2.21 1.06 - 1.87 - 0.43 - 1.52 0.98 - 2.95 1.32 - 3.04

			- >0 to <10 years - ≥10 to <20 years - ≥20 years ≥60 years: - No exposure - >0 to <10 years - ≥10 to <20 years - ≥20 years	- - - - - - -	- - - - - - -	- - - - - - -	- - - - - - -	0.81 OR 1.70 OR 2.01 OR 1.00 OR 1.11 OR 1.17 OR 1.04 OR	 - 0.56 - 2.19 0.57 - 2.39 0.70 - 1.54
Lucas 2013	Manual handling at least once during a working year.	None.	- No - Yes	1.0 OR 2.2	- 1.6 - 3.0	- -	- -	- -	- -
Palmer 2014	Exposure to lifting weights of at work.	Age groups, social class, smoking, digging/shovelling, and use of keyboard.	- No - approx. 9 kg - approx. 25 kg	1.00 PR 1.48 PR 1.64 PR	- 0.94 - 2.35 1.04 - 2.60	- - -	- - -	- - -	- - -
Other occupational mechanical exposures									
Descatha 2014	Years exposed to climbing stairs in working life (assessed on 2007).	Men: None.	- No - 1–15 years - >15 years	1.00 OR 0.91 OR 1.05 OR	- 0.69 – 1.19 0.85 – 1.31	- - -	- - -	- - -	- - -
	Exposure to climbing stairs (assessed in 2007)	Women: None.	- No - Yes	- -	- -	1.00 OR 1.15 OR	- 0.50 – 2.66	- -	- -
	Computer work (assessed in 1989).	None	- No - Yes	1.00 OR 0.99 OR	- 0.86 – 1.14	1.00 OR 1.02 OR	- 0.71 – 1.48	- -	- -
Palmer 2014	Exposure to digging/Shovelling at work.	Age.	- No - Yes	1.00 PR 1.87 PR	- 1.07 - 3.28	- -	- -	- -	- -
	Exposure to use of keyboard at work >4 hours.	Age	- No - Yes	1.00 PR 0.79 PR	- 0.42 - 1.46	- -	- -	- -	- -

BMI=body mass index; HDL=high-density lipoprotein; JEM=job-exposure matrix; LDL=low-density lipoprotein; O*NET= Occupational Information Network; OR=odds ratio; PR=prevalence ratio; TDI= townsend deprivation index.

Appendix 6. Funnel plots

Figure S1. Funnel plots of the three exposure categories.



Appendix 7. Scatterplots of exposure-response relations

Figure S2. Vibrations.

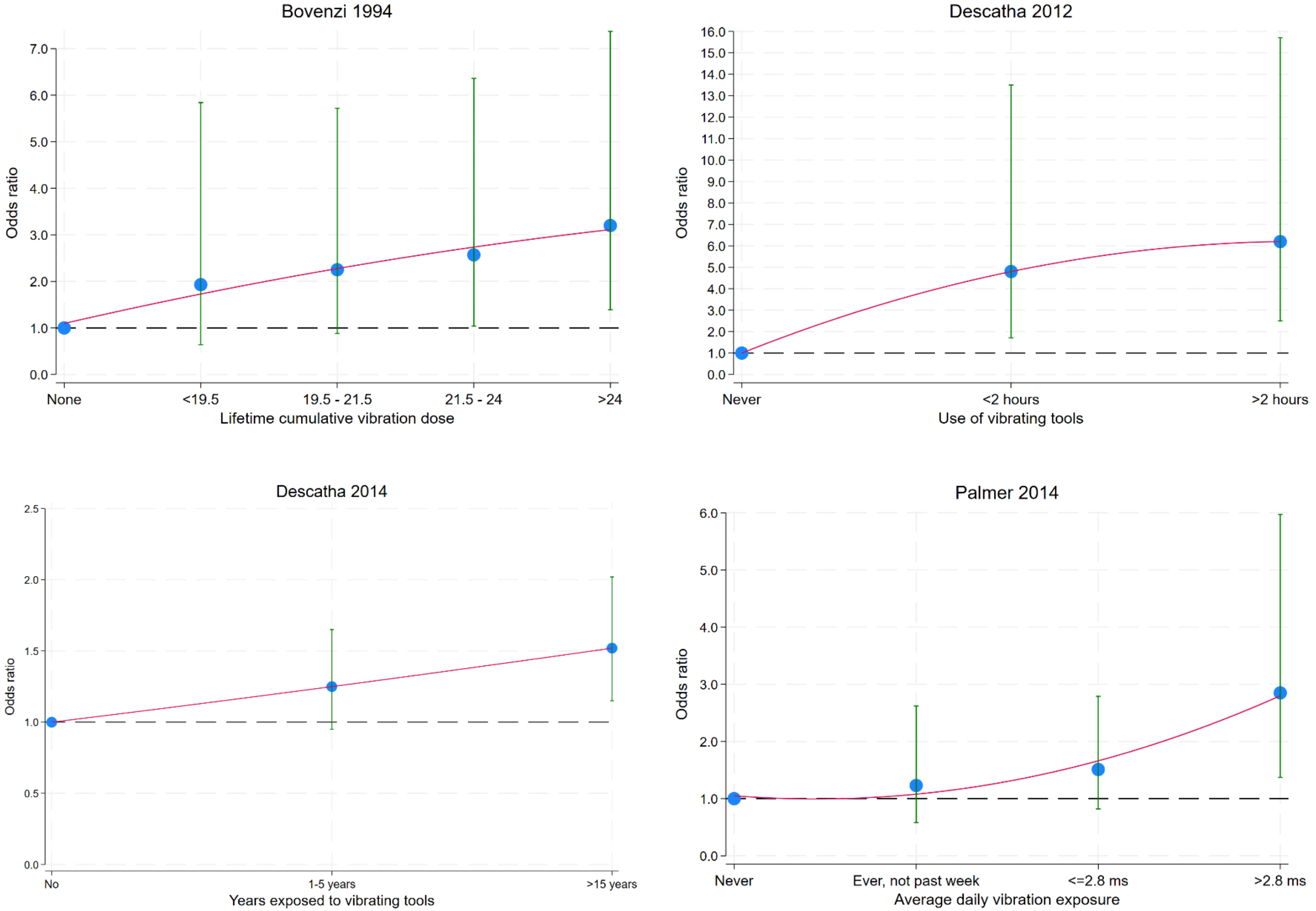


Figure S3. Combined mechanical exposures.

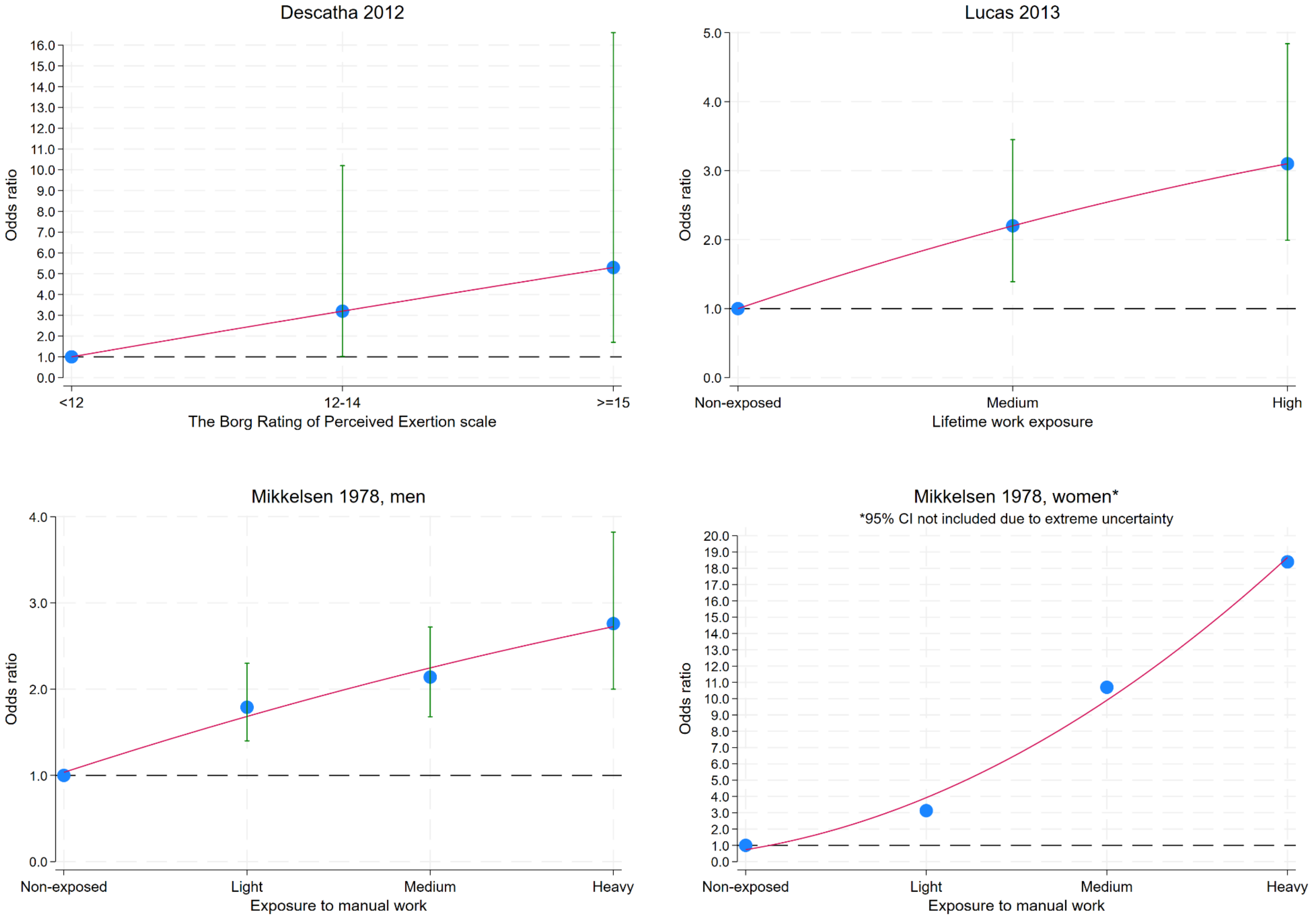


Figure S4. Lifting/carrying loads.