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FACTORS ASSOCIATED WITH THE DEVELOPMENT, PROGRESSION AND OUTCOME OF DUPUYTREN DISEASE TREATMENT: A SYSTEMATIC REVIEW

Luke Geoghegan MBBS BSc[1,2], Julian Man BSc[3], Abhilash Jain FRCS PhD[2], Andrew Price FRCS PhD[2], Elizabeth Gibbons MSc[4], Christina Jerosch-Herold PhD[5], Chris Gibbons PhD[6], Jeremy N Rodrigues FRCS PhD[2,7]

[1] Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London. London, UK

[2] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science (NDORMS), University of Oxford. Oxford, UK

[3] Imperial College School of Medicine. London, UK

[4] Nuffield Department of Population Health, University of Oxford. Oxford, UK

[5] School of Health Sciences, University of East Anglia. Norwich, UK

[6] Department of Symptom Research, Division of Internal Medicine, MD Anderson Cancer Centre, The University of Texas. Texas, USA

[7] Department of Plastic Surgery, Stoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust

Corresponding Author:

Jeremy N Rodrigues

NIHR Postdoctoral Fellow

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

University of Oxford

Windmill Road, Oxford

OX3 7HE

Email: jeremy.rodrigues@ndorms.ox.ac.uk

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ABSTRACT

Background

The factors typically considered to be associated with Dupuytren disease have been described, such as those in the “Dupuytren diathesis”. However, the quality of studies describing them has not been appraised. This systematic review aimed to analyse the evidence for all factors investigated for potential association with the development, progression, outcome of treatment or recurrence of Dupuytren disease.

Methods

A systematic review of MEDLINE, EMBASE and CINAHL was conducted using a PRISMA-compliant methodology up to September 2019. Articles were screened in duplicate. Prognostic studies were quality assessed using the Quality in Prognosis Study tool.

Results

This study identified 2,301 records; 51 met full inclusion criteria reporting data related to 54,491 patients with Dupuytren disease. In total, 46 candidate factors associated with the development of Dupuytren disease were identified. There was inconsistent evidence between the association of Dupuytren disease and the presence of ‘classical’ diathesis factors. The quality of included studies varied, and the generalisability of studies was low. There was little evidence describing the factors associated with functional outcome.

Conclusions

This systematic review challenges conventional notions of diathesis factors. Traditional diathesis factors are associated with disease development and recurrence although they are not significantly associated with poor outcome following intervention based on the current evidence.

INTRODUCTION

The term Dupuytren diathesis was first coined by Hueston, and comprised four factors: (1) bilateral palmar disease, (2) ectopic disease sites: over the dorsum of the knuckles (Garrod's pads), the feet (Ledderhose disease) and the penis (Peyronie's disease), (3) family history of Dupuytren Disease, and (4) ethnicity. [1] The presence of diathesis factors is purported to increase the risk of developing disease recurrence. [2]

Since Hueston's original description, a range of environmental [3] and patient-specific factors [4 5] have been proposed as being associated with Dupuytren disease. The addition of male gender and young age of onset to the classical diathesis factors increased the predictive risk of true recurrent Dupuytren to 71% compared to 23% in patients without any diathesis factors present. [6]

Identifying associations can involve different analyses. Univariable analyses look for an association between a single factor (e.g. male gender) and the outcome of interest (e.g. recurrence of Dupuytren disease). However, there may be confounding with other variables affecting such results. Multivariable analyses can account for confounding, by looking for the relationship between a factor (e.g. male gender) and an outcome (e.g. recurrence) while effectively removing the influence of one or more other factors (e.g. smoking).

While most clinical studies of Dupuytren disease treatment focused on recurrence as the primary outcome, some studies have assessed post-operative functional outcome. [7]

Functional outcome may encompass the impact of the disease itself and complications from treatment. [8] Thus, a bad functional outcome from surgery is possible without recurrence, and the factors associated with poor functional outcome may differ from those associated with recurrence.

Understanding which factors are associated with recurrence and poor post-operative outcomes can inform treatment decision-making and might allow targeting of supportive strategies.

This systematic review aimed to identify which factors that have been investigated for a potential association with the development, progression, recurrence or outcome of treatment in Dupuytren disease, and to appraise the quality of studies investigating these associations. We hypothesize

that while traditional diathesis risk factors may be associated with Dupuytren disease development and recurrence, they are not associated with functional outcome.

METHODS

The systematic review protocol was prospectively registered in the PROSPERO database (CRD42018087031). The design and reporting of the review followed the PRISMA statement. [9]

Search Strategy

A bespoke, sensitive search strategy, comprising of index (e.g. medical subject headings (MeSH) for OvidMedline) and free text terms, was designed in conjunction with a search strategist (**See Appendix, Supplemental Digital Content 1,** which shows the search strategies used for CENTRAL, EMBASE, Medline and CINAHL, INSERT HYPER LINK). The strategy was applied to Medline & In Process (1946- April 2018), EMBASE (1974- April 2018) and CINAHL (1981- April 2018). The search was updated on 26th September 2019. There were no restrictions in terms of language and date of publication. The British Society for Surgery of the Hand 2019 Autumn Meeting Abstracts were hand searched as a source of grey literature. [10]

Eligibility Criteria

Studies of any design presenting original data on multiple cases (randomised controlled trials (RCTs), non-randomised controlled trials, cohort studies, case-control studies and case series) were eligible for inclusion. Reviews, meta-analyses, descriptions of surgical technique, expert opinion and case reports were excluded.

Pre-specified stepwise inclusion criteria were applied by two co-authors (LG, JM), with conflicts resolved by a third reviewer (JNR).

Participants

Adults aged 18 years or older with clinically diagnosed Dupuytren disease were included.

Interventions and Comparators

The aim of the present review was not to determine intervention effectiveness. As such, all interventional procedures for Dupuytren contracture including needle fasciotomy (aponeurotomy), segmental aponeurectomy (very limited/ partial fasciectomy), limited fasciectomy,

dermofasciectomy and collagenase were included, if patients had undergone treatment. Observational clinical studies which did not involve interventions were also eligible for study inclusion, if they described the investigation of an association between one or more variables and a relevant aspect of Dupuytren disease clinical course.

Outcomes

All outcomes related to Dupuytren disease were considered. This included aspects related to the development, recurrence, or progression of the disease, as well as hand function and complications following intervention. Traditional diathesis factors were defined as bilateral and ectopic disease, Caucasian ethnicity and family history of disease. Genetic risk scores are individual patient scores calculated based on genotype at single-nucleotide polymorphisms associated with the development of Dupuytren disease. [11]

Study Selection

After compilation and electronic de-duplication, the titles and abstracts of retrieved studies were independently screened by two reviewers (LG, JM). Pre-specified stepwise inclusion criteria were implemented. Disagreements between reviewers were resolved through consultation with a third author (JNR).

Study classification

Within the included studies, predictive modelling studies were defined as those which aimed to examine the association between candidate variables and the outcome with a view to predicting the impact of that variable on the individual person. [12] In contrast, causal modelling studies were defined as those that analysed associations to test general causal hypotheses, rather than to build prediction models for individual people. [13]

Data Extraction and Analysis

Data extraction was performed electronically in duplicate (LG, JM). Study population demographics, intervention and control conditions, associated disease and patient specific factors, data related to disease progression and recurrence, reported outcomes (functional and patient

reported), and complications were extracted. Risk of bias for causal modelling studies that did not develop a model for individual prediction would be assessed using the Quality in Prognosis Study (QUIPS) tool. [14] Risk of bias for predictive modelling studies that aimed to develop a model for individual prediction would be assessed using the Prediction model Risk of Bias Assessment Tool (PROBAST). [15] The risk of bias for simple cohort studies would be assessed using the the National Institute of Health (NIH) quality assessment tool for cohort studies. RCTs would be assessed using the Cochrane Risk of Bias tool. [16] Non-full text records identified through the grey literature were not subject to full quality appraisal due to limited reporting and were distinguished in the presented analysis below. Narrative synthesis was planned.

RESULTS

Search results

A total of 2,301 records were identified from database searching. A further 360 studies were identified following the second search and 29 records were identified through searching the grey literature. Following electronic deduplication, 2,010 records were screened; 346 full text articles were assessed for study eligibility with 51 meeting full inclusion criteria (Figure 1). Details of the excluded studies are available on request.

Study characteristics

The 51 included studies comprised 45 cohort studies, 5 RCTs, and one case-control study. Collectively, 15 studies used multiple univariable statistical tests to determine the relationship between variables and outcomes, see Table 1. All cohort studies that used multivariable analysis met the definition of causal modelling studies. None of the included studies were classified as predictive modelling studies. [17] A further 33 studies used single univariable analyses to determine the relationship between variables and outcomes, see Table 2. The remaining 2 studies reported descriptive statistics only.

Study demographics and outcomes

A total of 54,491 patients with Dupuytren disease were included across all 51 included studies; 28 studies reported data on specific interventions for 2911 patients. Of those involving reported interventions, 61% underwent limited fasciectomy (1771/2911), 17% underwent segmental aponeurectomy (500/2911), 9% received collagenase (271/2911), 7% underwent needle fasciotomy (215/2911) and 5% underwent dermatofasciectomy (154/2911). A total of 46 patient, disease and treatment specific factors were studied, as summarised in Table 3.

Disease development, recurrence and progression

Classical diathesis factors

Collectively, 33 studies investigated association between conventional diathesis factors and disease development, recurrence and progression. The most frequently studied association was between family history and disease recurrence, as shown in the quilt plot (Figure 2). Eight studies used multivariable analysis and found significant associations between:

i. Family history with disease development [18,19], genetic risk scores [11,20], and recurrence [6,11,21].

ii. Ectopic disease with genetic risk scores [11,20,21] and disease recurrence [6,11].

iii. Bilateral disease with high genetic risk scores [11,20,21] and recurrence [6,11].

Non-classical diathesis factors

Eleven studies used multivariable analyses and found significant associations between the following non-diathesis factors and disease development, recurrence, and progression:

i. Older age [22,23], high alcohol intake (> 5 glasses of wine/beer or >3 glasses of spirits per day [23], 'alcoholism' [18] and 'high daily alcohol intake'[18,19,23]), diabetes [18,19,23], gender [19,22,23], hypercholesterolaemia [19], ischaemic heart disease [19], occupation [18,19,22,23], previous hand trauma [18] and Tubiana stage [19] with disease development.

ii. Age [11,20,21], hypertension [21], smoking [21] and genetic risk.

iii. Age [19,24], alcohol intake [19], gender [19,24], affected fingers [24] and disease progression.

iv. Age [6,11], alcohol intake [6], degree of baseline contracture [25], disease affecting the MCPJ [25], disease affecting the PIPJ [26], affected fingers [25], gender [6], smoking [6], treatment type [26] and disease recurrence.

In all other studies which used multivariable analyses, no significant association between variables and disease development, progression and recurrence were found at $p<0.05$. The remaining studies which investigated association between conventional diathesis factors and disease development, recurrence and progression using univariable analyses are outlined in table 3.

Disease outcome

Classical diathesis factors

Sixteen studies investigated the association between conventional diathesis factors and disease outcome. Reported outcomes included patient-reported outcome measures such as the Disabilities of the Arm, Shoulder and Hand score (DASH), quickDASH, the Michigan Hand Outcomes Questionnaire (MHQ), the Unité Rhumatologique des Affections de la Main (URAM), the EQ5D, and other functional measures such as grip strength, range of motion and joint angles, and complications.

Three studies used multivariable analyses and found no significant association between classical diathesis factors and complications, patient-reported and other functional outcomes [27-29].

Non classical-diathesis factors

Six studies used multivariable analyses and found significant associations between the following non-diathesis factors and outcome:

i. Age, alcohol intake, diabetes, occupation and self-reported disability [23]
ii. Diabetes [27], gender [27], emotional factors [28] and previous surgery [27] with DASH scores
iii. Age [24], gender [24], type of intervention [25], Tubiana stage [24] and length of follow up [25] with joint angle correction
iv. Type of intervention and complications [27]

Across all other factors, 16 studies used univariable analyses and found significant associations between:

i. Type of intervention and self-reported disability [30]
ii. Baseline contracture [31], gender [32], length of follow up [26,33], MCPJ disease [34], affected digits [33] and treatment type [30,35,36] with DASH/quickDASH scores
iii. Length of follow up and EQ-5D scores [33]
iv. Baseline contracture and grip strength [36]
v. Length of follow up [26,37], MCPJ disease [38], PIPJ disease [38], affected fingers [39] and treatment type [26,30,36,40,41] with joint angle correction
vi. Baseline contracture [42,43], PIPJ disease [44] and smoking [45] with complications

vii. Affected fingers and range of motion [39]

In all other studies which used univariable analyses, no significant association between variables and outcome were found at $p<0.05$.

Quality of included studies

All multivariable analysis studies had moderate to high risk of bias, based on the QUIPS tool. Specifically, 70% of included studies were deemed to have a high risk of selection bias and 62% were deemed to have a high risk of bias due to confounding (**see Table, Supplemental Digital Content 2**, which shows the quality of included prognostic cohort studies which utilized multiple univariate analysis assessed using the Quality In Prognosis Study (QUIPS) tool), INSERT HYPER LINK).

All other cohort studies that implemented univariable analyses were assessed using the National Heart, Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Of the included studies 66% were rated as fair (**see Table, Supplemental Digital Content 3**, which shows the quality of included cohort studies assessed using the National Heart, Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, INSERT HYPER LINK).

DISCUSSION

This systematic review aimed to identify all factors investigated for an association with the development, recurrence, progression and outcome of Dupuytren's disease. The causal modelling studies identified did not demonstrate an association between traditional diathesis factors and functional measures of disease outcome. This cautions against extending the assumption that traditional diathesis factors will be associated with all kinds of poor outcome following intervention. Instead, the existing evidence suggests that distinct, non-diathesis factors are associated with poor functional outcome following intervention. This is likely to have importance from the perspective of patients, healthcare commissioners, and surgeons alike.

Genome wide association studies have identified susceptibility loci and suggest aberrations in the Wnt-signalling pathway may confer increased risk of disease development. [46,47] Previous work has demonstrated that individuals with a high genetic risk score (high number of alleles known to increase risk of disease development) is significantly associated with the presence of all traditional diathesis factors (early age of onset, a positive family history, bilateral and ectopic disease. [11] It is known that several genetic and environmental risk factors are involved in disease pathogenies, however it is not well-known which factors are associated with outcome following intervention.

Understanding which factors are associated with disease development or progression, or with treatment outcome, is valuable in both research and in clinical practice. Many candidate factors are not straightforward to measure. For example, "smoking" may vary by type of tobacco product used, number of cigarettes smoked (which itself is likely to fluctuate over a lifetime), and ex-smoker status (which may apply to those stopped smoking a week ago, or a decade ago). In contrast, conventional diathesis factors are all "fixed". This might make it easier to suspect them, and then to study them.

Evaluating the associations in this review requires careful consideration of the dependent variables being studied. The robustness and usefulness of the different outcomes/disease parameters may vary. For example, "true" recurrence (defined as development of new Dupuytren disease tissue in

the same site as previous surgery) has been acknowledged as being at high risk of detection bias. This relates to the subjective binary nature of recurrence, especially with unblinded assessors. [48]

Other studies used broader definitions of recurrence. An example included here was having two or more surgeries on the same hand. [21] There may be limitations to this too. It may represent a combination of true recurrence, false recurrence (due to scar and joint contracture), or extension of disease (development of new Dupuytren disease away from the area of surgery). It also requires the patient with true recurrence to be offered further treatment by a surgeon, and to agree to go ahead with it. Thus, it will not include all patients who have had a functionally relevant recurrence, but have either been denied further treatment, or who have declined it.

Furthermore, some interventions such as fasciotomy do not clear diseased tissue, and recurrence is likely to increase with longer follow up periods given the chronicity of the condition. These variations in how recurrence is defined, and how reliably it is assessed, will have consequences for similar issues faced when using angular joint measurement to determine disease progression.

Further challenges exist with understanding which factors are associated with treatment outcome. We demonstrated marked variation in the functional outcome measures used, only some of which have been validated, and even those have limitations to their validity. These ranged from asking participants bespoke questions like ‘do you have any limitations [because of Dupuytren disease]’, to the DASH, which is the most commonly used PROM across all studies of electively managed hand conditions including Dupuytren [49], and was used in 14 studies here. Other PROMs studied include the EQ-5D in two (a measure of health status) [50], the Unite Rhumatologique des Affections de la Main (URAM) scale (a Dupuytren disease-specific PROM) [51], and the Michigan Hand Outcomes Questionnaire (a hand-specific PROM) [52].

As well as this variation in the measurement tools used, and the underlying constructs that they assess, other variables may affect patients’ responses. One study included here considered emotional functions, not captured in the DASH. These were significantly associated with improvements in DASH scores following intervention. This may be due to the fact that factors such as anxiety about coping with activities of daily living and occupational demands are not captured

in patient reported outcome measures such as the DASH despite being identified as important to patients. [53]

Thus, there are limitations and inconsistencies in the results included here. The majority of the included analyses were at risk of bias, either from issues in multivariable analysis studies, where confounding might otherwise be well-controlled, or because only univariable analysis was performed, without control of confounding.

What can be concluded from the results of this review is that our best estimates suggest that different factors are associated with different elements of Dupuytren disease natural history and treatment. The Dupuytren diathesis factors may be applicable to disease development and some definitions of recurrence, but other factors may be more relevant to measure and account for when studying functional outcome and complications of treatment. The reliability of the evidence available, and the strength of associations should also be considered, and not necessarily accepted at face value. Further evidence is likely to increase our confidence in this area. Inconsistent outcome use and incomplete reporting of results limits the synthesis of data from existing studies; defining consensus-based core outcome sets for Dupuytren disease could reduce this issue and enable consensus regarding what constitutes a 'good' outcome following intervention to be reached. Further work to clarify the association between factors and disease outcome would be helpful. Pragmatically this could be achieved through big data analysis of core outcomes collected in national registries or similar datasets. Once candidate factors for good or bad outcomes following intervention have been identified, the Bradford Hill Criteria could be applied to establish causal inference. [54] Such criteria should not be seen as a rigid framework but integrated into a wider causal inference toolset. Larger registry-based datasets should be evaluated for consistency amongst exposure and outcome. This data can be used in conjunction with data from studies investigating the genomic and molecular pathogenesis to examine biological plausibility and temporality of exposure and disease outcome.

Our results must be considered in view of the study limitations. Although a sensitive search strategy was used, it is possible that relevant publications may have been overlooked. Further, due to the

heterogeneity of included studies and variety of outcome measures, it was not possible to perform quantitative synthesis. This review presents data from studies conducted around the world and as such may not be generalisable to a specific population. Information on specific interventions was reported for 2911 patients identified in our systematic review, although only 28 out of 51 included studies reported the type of intervention used. The paucity of data describing specific interventions may be due to inclusion of large studies which aim to determine factors associated with recurrence using national datasets[11]. Further primary studies should seek to report clinically relevant parameters identified in this review. Studies that do not report intervention type have been included in the present review as exclusion of such studies may predispose to selection bias. Further, causal inference of identified associations must be determined before definitive conclusions regarding the effect of identified factors on disease development, recurrence and outcome can be made.

In summary, this review demonstrates that the evidence supporting the association of traditional diathesis factors with the development and recurrence of Dupuytren disease is at risk of bias. Other factors may be associated with poor functional outcome and complications following intervention for Dupuytren disease. The results of this systematic review may be used in the clinical setting when counselling patients on factors associated with risks of recurrence and poor functional outcome following intervention. Further evidence is likely to increase our confidence of which factors affect the development and outcome of Dupuytren disease and its treatment.

FIGURE LEGEND

Figure 1: PRISMA flow chart

Figure 2: Quilt plot demonstrating the absolute number of included studies which investigated association between classical diathesis factors and disease development, progression, recurrence and outcome.

SUPPLEMENTAL DIGITAL CONTENT LEGEND

Appendix, Supplemental Digital Content 1: Search strategies used for CENTRAL, EMBASE, Medline and CINAHL

Table, Supplemental Digital Content 2: Quality of included prognostic cohort studies which utilized multiple univariate analysis assessed using the Quality In Prognosis Study (QUIPS) tool.

Table, Supplemental Digital Content 3: Quality of included cohort studies assessed using the National Heart, Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

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Table 1

Table 1: Summary of papers which used multivariable analyses to determine the relationship between risk factors, disease development, recurrence and outcomes.

Article	Study Design	Description	N patients (hands)	Risk of bias
Anwar 2007	Cohort	Univariable analysis used to examine differences in joint involvement and correction between men and women. Multivariable regression used to determine relationship between factors, recurrence and degree of contracture.	109 (119)	High risk
Becker 2015	Cohort	Multivariable analysis used to determine relationship between factors, genetic risk (as per positive family history), recurrence and progression.	801 (1001)	High risk
*Broekstra 2019**	Cohort	Logistic lasso regression analysis used to determine predictors of disease progression.	258	-
Descatha 2014	Cohort	Univariable and multivariable analysis used to determine relationship between factors, disease development and self-reported disability.	839	High risk
Dolmans 2012	Cohort	Multivariable analysis used to determine relationship between factors and a high genetic risk score in patients with diagnosed Dupuytren's.	566	Moderate risk
Engstrand 2015	Cohort	Univariable analysis used to determine differences in demographic and disease specific factors and DASH score. Multivariable regression analysis used to determine relationship between factors and DASH score.	81	Moderate risk
Hindocha 2006 ii	Cohort	Multivariable analysis used to calculate adjusted odds for factors which increase recurrence.	322	Moderate risk
Marques 2002	Cohort	Logistic regression used to determine relationship between variables and the development of Dupuytren's disease versus a matched control cohort.	125	Moderate risk
Morelli 2017	Case-control study	Univariable used to determine the relationship between factors and disease development. Multivariable analysis used to determine relationship between factors, development and progression.	59	High risk
Nordenskjold 2019	Cohort	Predictors of recurrence analysed using logistic regression model adjusted for gender and age.	83	Moderate risk
Palmer 2014	Cohort	Multivariable analysis used to determine relationship between factors, development and progression.	72	Moderate risk
Reismeijer 2019	Cohort	Univariable logistic regression used to develop a weighted genetic risk score for predicting need for further surgical intervention	7856	Moderate risk

Rodrigues 2016	Cohort	Univariable was used to compare objective outcomes and adverse events between treatment arms. Multivariable analysis used to calculate adjusted odds ratios for factors associated with impaired function and adverse outcomes.	413	Moderate risk
Scheibler 2019	Cohort	Multivariable analysis used to determine factors predicting outcomes following treatment with Colleganse.	92	Moderate risk
Selles 2018	RCT	Univariable analysis used to determine differences in outcome between patients treated with percutaneous aponeurotomy and limited fasciectomy. Multivariable analysis used to determine relationship between factors and recurrence.	52	Fair

DASH- Disabilities of the Arm, Shoulder and Hand score

* Non full text record identified through the grey literature.

Table 2: Summary of papers which used univariable analysis to determine the relationship between risk factors, disease development, recurrence and outcomes.

Reference	Study Design	Description	N patients	Evidence quality
Abe 2004 i	Cohort	Univariable analysis used to determine relationship between factors and disease recurrence.	57	Fair
Abe 2004 ii	Cohort	Univariable analysis used to determine relationship between risk factors and recurrence in patients with either radial or ulnar disease exclusively.	77	Fair
Abe 2004 iii	Cohort	Univariable analysis used to determine relationship between factors and recurrence after fasciectomy. Odds ratios for recurrence were determined and a function was defined based on discriminant analysis.	65	Fair
Abe 2015	Cohort	Univariable analysis used to determine relationship between factors, recurrence and objective function following percutaneous needle fasciotomy. Odds ratio for each factor and disease recurrence described.	51	Fair
Adam 1992	Cohort	Univariable analysis used to determine relationship between factors and recurrence following fasciectomy.	85	Fair
Atroshi 2015	Cohort	Univariable analysis used to determine relationship between factors and complications following treatment with collagenase.	146	Good
Badalamente 2007	RCT	Univariable analysis used to determine relationship between factors and complications following treatment with collagenase. Kaplan-Meier method and log-rank test used to compare outcomes between treatment groups.	33	Fair
Bergovec 2018	Cohort	Univariable analysis used to determine relationship between factors and disease recurrence following fasciectomy.	34	Fair
Bradlow 1986	Cohort	Univariable analysis used to determine relationship between alcohol and disease development.	64	Fair
Budd 2011	Cohort	Univariable analysis were used to determine relationship between factors, objective hand function, grip strength and quickDASH scores. Pearson's correlation coefficient used to determine relationship between objective functional measures and quickDASH scores.	69	Fair
Coert 2006	Cohort	Univariable analysis was used to determine the relationship between factors, progression, recurrence and complications following fasciectomy.	261	Fair
Degreef 2009	Cohort	Spearman's correlation coefficient used to determine relationship between DASH scores and objective measures of hand function.	80	Poor
Dias 2013	Cohort	Univariable analysis used to determine relationship between factors and recurrence following fasciectomy.	63	Fair
Engstrand 2009	Cohort	Univariable analysis used to determine demographic differences between study participants and drop outs as well as self-reported disability and DASH before and after intervention. Spearman's Correlation Coefficient was used to determine the relationship between DASH scores and objective function.	60	Fair
Engstrand 2014	Cohort	Univariable analysis used to determine differences in demographic factors between single and multi-digit cohort. Factorial ANOVA used to determine significant differences in DASH/EQ-5D/ROM between single and multi-digit cohorts over time.	82	Good
Fei 2019	Cohort	Univariable analysis used to determine differences in joint contracture before and after Collagenase	21	Fair
Ferry 2013	Cohort	Univariable analysis used to determine differences in development, recurrence, disease progression and outcome between genders.	136	Fair
Grandizio 2017	Cohort	Descriptive statistics used for demographics, disease characteristics, co-morbidities, treatment outcomes and complications in the cohort.	31	Fair

Gudmundsson 2001	Cohort	Univariable analysis used to determine association between alcohol consumption, disease development and progression.	193	Fair
Hindocha 2006 i	Cohort	Univariable analysis used to determine association between multiple factors and a positive family history.	62	Fair
Jerosch-Herold 2011	Cohort	Pearson Correlation Coefficients used to determine association between DASH scores and flexion contracture, total active flexion and total active motion.	154	Good
Kitridis 2019	Cohort	Univariable analysis used to determine pre-operative and follow up quickDASH scores as well as grip strength between affected and unaffected hands.	30	Fair
Moermans 1997	Cohort	Follow-up life table analysis used to analyse recurrence following surgery. Mathematical model created to predict the number of cases of recurrence.	141	Poor
Nayar 2019	Cohort	Univariable analysis used to determine improvement in joint contracture and recurrence.	34	Fair
Rebelo 1995	Cohort	Univariable analysis used to determine association between demographic factors and co-morbidities on disease recurrence.	110	Poor
Scherman 2018	RCT	Univariable analysis used to determine association between outcomes in patients treated with needle fasciotomy and collagenase.	93	Fair
Simon-Perez 2018	Cohort	Univariable analysis used to determine relationship between factors, disease recurrence, progression and complications.	71	Good
Stromberg 2018	RCT	Univariable analysis used to determine association between outcomes and complications in patients treated with fasciotomy and collagenase	156	Good
Skov 2017	RCT	Univariable analysis used to determine relationship between patients treated with collagenase and fasciotomy with respect to disease outcome, recurrence and complications	50	Fair
van Rijssen 2012	Cohort	Univariable analysis used to determine relationship between factors and disease recurrence following treatment with percutaneous needle fasciotomy.	30	Fair
van Giffen 2006	Cohort	Univariable analysis used to describe outcomes and recurrence rates following limited fasciectomy, segmental fasciectomy and dermatofasciectomy.	38	Fair
Wade 2016	Cohort	Univariable analysis used to determine differences in baseline characteristics and outcomes between patients either undergoing single digit fasciectomy or dermatofasciectomy. Odds ratios for dermal involvement calculated.	103	Good
Weckesser 1964	Cohort	Univariable analysis used to determine the relationship between factors and recurrence following fasciectomy.	81	Poor
Zyluk 2007	Cohort	Univariable analysis used to determine the relationship between factors, DASH scores and functional outcomes following fasciectomy.	54	Fair

ANOVA- Analysis of Variance; **DASH-** Disabilities of the Arm, Shoulder and Hand score; **EQ-5D-** EuroQol 5 dimensions; **ROM-** Range of motion

Table 3: Overview of associations between factors and outcomes investigated in included studies.

	Development					Outcome								
	Ulnar disease	**Radial disease**	**Genetic risk**	**Disease progression**	**Disease recurrence**	**Self-reported disability**	**DASH/ qDASH**	**MHQ**	**EQ-5D**	**URAM**	**Grip strength**	**Joint angle**	**Complication of treatment**	**Range of motion**
Abe's diathesis score					Van Rijssen 2012 (?) Abe 2015 (-)									
Adhesive capsulitis			Hindocha 2006.i (-)		**Hindocha 2006.ii (-)**									
Age	**Palmer 2014 (+)** Gudmundsson 2011 (-) **Descatha 2014 (+)** Broekstra 2019.ii (?)*	Abe 2004.ii (-)	**Riesmeijer 2019 (+)** **Dolmans 2012 (+)** Hindocha 2006.i (+) **Becker 2015 (+)**	Simon-Perez 2018 (-) Engstrand 2014 (?) **Morelli 2017 (+)** **Anwar 2007 (+)** **Broekstra 2019.i (?)***	Simon-Perez 2018 (-) Stromberg 2018 (?) Van Rijssen 2012 (-) **Nordenskjold 2019 (?)** **Riesmeijer 2019 (+)** Kitridis 2019 (-) Scherman 2018 (?) Skov 2017 (?) Abe 2015 (+) Dias 2013 (-) **Hindocha 2006.ii (+)** Abe 2004.i (+) Abe 2004.iii (+) Adam 1992 (-) **Morelli 2017 (-)** **Anwar 2007 (-)** Moermans 1997 (+) Rebelo 1995 (+) Weckesser 1964 (?)	**Descatha 2014 (+)**	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Selles 2018 (?) Skov 2017 (?) **Rodrigues 2016 (-)** **Engstrand 2015 (-)** Bergovec 2018 (-) Engstrand 2009 (?) Zyluk 2007 (-) Degreef 2009 (?)	**Scheible r 2019 (-)**	Engstrand 2014 (?)	Stromberg 2018 (?)	Zyluk 2007 (?)	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Fei 2019 (?) Bergovec 2018 (-) Skov 2017 (?) Budd 2011 (?) Van Giffen 2006 (-) Zyluk 2007 (?) **Anwar 2007 (+)** **Broekstra 2019.i (?)***	Simon-Perez 2018 (?) Atroshi 2015 (-) Skov 2017 (?) **Rodrigues 2016 (?)** Weckesser 1964 (?)	Jerosch-Herold 2011 (?)
Alcohol	Gudmundsson 2011 (-) Coert 2006 (?) Bradlow 1986 (+) **Descatha 2014 (+)** **Marques 2002 (+)**	Abe 2004.ii (-) **Morelli 2017 (+)**	Gudmundsson 2011 (-) Hindocha 2006.i (-) **Becker 2015 (-)**	Gudmundsson 2011 (-) Bozhanina 2016 (-) **Morelli 2017 (+)**	Kitridis 2019 (?) Skov 2017 (?) Dias 2013 (-) **Hindocha 2006.ii (+)** Van Giffen 2006 (-) Abe 2004.iii (-) Adam 1992 (-) **Morelli 2017 (-)** Moermans 1997 (-) Rebelo 1995 (-)	**Descatha 2014 (+)**	Kitridis 2019 (?) Bergovec 2018 (?) Skov 2017 (?) **Rodrigues 2016 (-)**				Kitridis 2019 (?)	Grandizio 2017 (?) Skov 2017 (?) Van Giffen 2006 (?)	Grandizio 2017 (?) Skov 2017 (?) **Rodrigues 2016 (?)**	
Anti-convulsant drugs	Bradlow 1986 (-) **Morelli 2017 (?)**	**Morelli 2017 (?)**		**Morelli 2017 (?)**	**Morelli 2017 (-)**									
Baseline contracture			**Dolmans 2012 (-)** Hindocha 2006.i (+)		Wade 2016 (?) Van Rijssen 2012 (-) **Nordenskjold 2019 (+)** Weckesser 1964 (+)		Jerosch-Herold 2011 (+) Engstrand 2009 (-) Zyluk 2007 (-) Degreef 2009 (-)	**Scheible r 2019 (-)**			Zyluk 2007 (+)	Zyluk 2007 (-) Van Giffen 2006 (-)	Atroshi 2015 (+) Grandizio 2017 (+)	
Bilateral disease		Abe 2004.ii (+)	**Riesmeijer 2019 (+)** **Dolmans 2012 (-)** **Becker 2015 (+)**	Engstrand 2014 (+)	**Riesmeijer 2019 (+)** Dias 2013 (-) **Hindocha 2006.ii (-)** Van Giffen 2006 (-) Abe 2004.iii (+)		**Engstrand 2015 (?)** Engstrand 2009 (?) Zyluk 2007 (?) Degreef 2009 (-)		Engstrand 2014 (?) **Engstrand 2015 (?)**		Zyluk 2007 (?)	Badalamente 2007 (?) Grandizio 2017 (?) Van Giffen 2006 (?) Zyluk 2007 (?)	Grandizio 2017 (?)	**Engstrand 2015 (?)**
Cancer				**Broekstra 2019.i (-)***								**Broekstra 2019.i (-)***		
CTS					**Hindocha 2006.ii (-)**									
Cirrhosis	Coert 2006 (?)		Hindocha 2006.i (-)											
Diabetes	Coert 2006 (?) Bradlow 1986 (-) **Marques 2002 (+)** **Descatha 2014 (+)** **Morelli 2017 (+)**	Abe 2004.ii (-)	Hindocha 2006.i (-) **Becker 2015 (-)**	Engstrand 2014 (?)	Stromberg 2018 (?) Van Rijssen 2012 (?) Kitridis 2019 (?) Skov 2017 (?) Dias 2013 (-) Van Giffen 2006 (-) **Hindocha 2006.ii (-)** Abe 2004.i (-) Abe 2004.iii (-) Rebelo 1995 (-) Weckesser 1964 (-)	**Descatha 2014 (+)**	Stromberg 2018 (?) Kitridis 2019 (?) Selles 2018 (?) Skov 2017 (?) **Rodrigues 2016 (+)** **Engstrand 2015 (?)** Bergovec 2018 (?) Engstrand 2009 (?) Zyluk 2007 (?)		Engstrand 2014 (?) **Engstrand 2015 (?)**	Stromberg 2018 (?)	Kitridis 2019 (?) Zyluk 2007 (?)	Stromberg 2018 (?) Grandizio 2017 (?) Skov 2017 (?) Van Giffen 2006 (?) Zyluk 2007 (?)	Grandizio 2017 (?) Skov 2017 (?) **Rodrigues 2016 (?)** Weckesser 1964 (?)	**Engstrand 2015 (?)**
DIPJ disease												O'Brien 2019 (?)*	Coert 2006 (-)	

Ectopic disease (unspecified)			Riesmeijer 2019 (+)		Van Rijssen 2012 (-) Riesmeijer 2019 (+) Badalamente 2007 (?) Hindocha 2006.ii (-) Abe 2004.i (+) Moermans 1997 (+) Rebelo 1995 (+)	Selles 2018 (?)							
Emotional function						Engstrand 2015 (+)							
Ethnicity	Morelli 2017 (?)	Morelli 2017 (?)	Hindocha 2006.i (?)	Morelli 2017 (?)	Hindocha 2006.ii (?) Morelli 2017 (-)						Grandizio 2017 (?)	Grandizio 2017 (?)	
Epilepsy	Coert 2006 (?)	Abe 2004.ii (-)	Hindocha 2006.i (-)		Van Rijssen 2012 (?) Skov 2017 (?) Dias 2013 (-) Hindocha 2006.ii (-) Van Giffen 2006 (-) Abe 2004.i (-) Abe 2004.iii (-) Moermans 1997 (-) Rebelo 1995 (-)	Skov 2017 (?)					Grandizio 2017 (?) Skov 2017 (?) Van Giffen 2006 (?)	Grandizio 2017 (?) Skov 2017 (?)	
Family history	Coert 2006 (?) Marques 2002 (+) Bradlow 1986 (-)	Morelli 2017 (+)	Riesmeijer 2019 (+) Dolmans 2012 (+)	Engstrand 2014 (?) Becker 2015(+) Broekstra 2019.i (-)*	Stromberg 2018 (?) Wade 2016 (?) Riesmeijer 2019 (+) Skov 2017 (?) Dias 2013 (-) Badalamente 2007 (?) Hindocha 2006.ii (-) Van Giffen 2006 (-) Abe 2004.i (-) Abe 2004.iii (-) Adam 1992 (-) Becker 2015 (+) Moermans 1997 (-) Rebelo 1995 (-) Weckesser 1964 (+)	Stromberg 2018 (?) Selles 2018 (?) Skov 2017 (?) Rodrigues 2016 (-) Engstrand 2015 (?)		Engstrand 2014 (?) Engstrand 2015 (?)	Stromberg 2018 (?)		Stromberg 2018 (?) Grandizio 2017 (?) Skov 2017 (?) Badalamente 2007 (?) Van Giffen 2006 (?) Broekstra 2019.i (-)*	Grandizio 2017 (?) Skov 2017 (?) Rodrigues 2016 (?) Weckesser 1964 (?)	Engstrand 2015 (?)
Gender	Palmer 2014 (-) Bradlow 1986 (?) Morelli 2017 (+) Descatha 2014 (?) Broekstra 2019.ii (?)*		Hindocha 2006.i (-) Becker 2015 (-)	Simon-Perez 2018 (?) Engstrand 2014 (?) Coert 2006 (+) Morelli 2017 (+) Anwar 2007 (-) Broekstra 2019.i (?)*	Simon-Perez 2018 (?) Stromberg 2018 (?) Wade 2016 (?) Van Rijssen 2012 (?) Nordenskjold 2019 (?) Kitridis 2019 (?) Scherman 2018 (?) Skov 2017 (?) Hindocha 2006.ii (+) Coert 2006 (-) Abe 2004.i (-) Adam 1992 (-) Morelli 2017 (-) Anwar 2007 (-) Moermans 1997 (-) Rebelo 1995 (?)	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Kitridis 2019 (?) Selles 2018 (?) Rodrigues 2016 (+) Engstrand 2015 (?) Ferry 2013 (+) Engstrand 2009 (?) Zyluk 2007 (?) Degreef 2009 (?)	Scheible r 2019 (-)	Engstrand 2014 (?) Engstrand 2015 (?)	Stromberg 2018 (?)	Kitridis 2019 (?) Zyluk 2007 (?)	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Fei 2019 (?) Grandizio 2017 (?) Ferry 2013 (+) Budd 2011 (?) Zyluk 2007 (?) Van Giffen 2006 (-) Anwar 2007 (+) Broekstra 2019.i (?)*	Simon-Perez 2018 (?) Atroshi 2015 (-) Grandizio 2017 (?) Rodrigues 2016 (?) Anwar 2007 (-)	Jerosch-Herold 2011 (?) Engstrand 2015 (?)
Hand dominance				Engstrand 2014 (?)	Stromberg 2018 (?) Wade 2016 (?) Kitridis 2019 (?) Skov 2017 (?)	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Kitridis 2019 (?) Skov 2017 (?) Rodrigues 2016 (?) Engstrand 2015 (?) Budd 2011 (-) Zyluk 2007 (?) Degreef 2009 (?)		Engstrand 2014 (?) Engstrand 2015 (?)	Stromberg 2018 (?)	Kitridis 2019 (?) Zyluk 2007 (?)	Stromberg 2018 (?) Jerosch-Herold 2011 (?) Grandizio 2017 (?) Skov 2017 (?) Budd 2011 (-) Zyluk 2007 (?)	Grandizio 2017 (?) Skov 2017 (?) Rodrigues 2016 (?)	Jerosch-Herold 2011 (?) Engstrand 2015 (?) Budd 2011 (-)
High cholesterol	Coert 2006 (?)	Morelli 2017 (+)	Hindocha 2006.i (-)										
HIV											Grandizio 2017 (?)	Grandizio 2017 (?)	
Hypertension			Becker 2015 (+)										
IHD	Morelli 2017 (+)												
Knuckle pads		Abe 2004.ii (+)	Dolmans 2012 (+) Becker 2015 (+)		Hindocha 2006.ii (+) Van Giffen 2006 (-) Abe 2004.iii (+) Weckesser 1964 (?)	Rodrigues 2016 (-)					Badalamente 2007 (?) Van Giffen 2006 (?)	Rodrigues 2016 (?) Weckesser 1964 (?)	
Lederhosen disease	Coert 2006 (?) Morelli 2017 (?)	Abe 2004.ii (+) Morelli 2017 (?)	Dolmans 2012 (+) Becker 2015 (+)	Morelli 2017 (?)	Kitridis 2019 (?) Skov 2017 (?) Hindocha 2006.ii (-) Van Giffen 2006 (-)	Kitridis 2019 (?) Skov 2017 (?) Selles 2018 (?) Selles 2018 (?)				Kitridis 2019 (?)	Grandizio 2017 (?) Skov 2017 (?) Badalamente 2007 (?) Van Giffen 2006 (?)	Grandizio 2017 (?) Skov 2017 (?) Weckesser 1964 (?)	

					Abe 2004.iii (+) **Morelli 2017 (-)** Weckesser 1964 (?)		Bergovec 2018 (?)										
Length of follow up					Adam 1992 (+)		Engstrand 2014 (+) Selles 2018 (+) **Rodrigues 2016 (-)**		Engstrand 2014 (+)				**Nordenskjold 2019 (+)** Skov 2017 (?) Scherman 2018 (+) Selles 2018 (+)		**Rodrigues 2016 (?)**		
Little finger disease					Stromberg 2018 (?) Van Rijssen 2012 (-) Abe 2004.i (-) Abe 2004.iii (+) Adam 1992 (+)		Stromberg 2018 (?) **Rodrigues 2016 (-)** Engstrand 2009 (?)			Stromberg 2018 (?)			Stromberg 2018 (?)				
MCPJ disease					Stromberg 2018 (?) **Nordenskjold 2019 (+)** Abe 2015 (+)		Stromberg 2018 (?) Bergovec 2018 (+) Selles 2018 (?) Engstrand 2009 (?) Degreef 2009 (-)	**Scheible r 2019 (-)**		Stromberg 2018 (?)			Stromberg 2018 (?) Badalamente 2007 (+) O'Brien 2019 (?)*		Coert 2006 (-)		
Meniere's disease	Coert 2006 (?)																
Menopause	Ferry 2013 (-)				Ferry 2013 (-)												
Operated fingers			**Dolmans 2012 (-)**	Engstrand 2014 (?) **Anwar 2007 (+)**	**Nordenskjold 2019 (+)** Scherman 2018 (?) Skov 2017 (?) Dias 2013 (-) Abe 2004.iii (-) Adam 1992 (+) **Anwar 2007 (-)** Moermans 1997 (-) Weckesser 1964 (+)		Engstrand 2014 (+) Jerosch-Herold 2011 (?) Bergovec 2018 (-) Selles 2018 (?) Skov 2017 (?) **Rodrigues 2016 (?)** **Engstrand 2015 (?)** Engstrand 2009 (?) Zyluk 2007 (-) Degreef 2009 (-)		Engstrand 2014 (?) **Engstrand 2015 (?)**		Zyluk 2007 (-)	Jerosch-Herold 2011 (?) Fei 2019 (?) Grandizio 2017 (?) Skov 2017 (?) Budd 2011 (+) Zyluk 2007 (?)		Grandizio 2017 (?) Skov 2017 (?) **Rodrigues 2016 (?)**		Jerosch-Herold 2011 (?) **Engstrand 2015 (?)** Budd 2011 (+)
Occupation	**Palmer 2014 (+)** **Marques 2002 (-)** **Morelli 2017 (+)** **Descatha 2014 (+)**		Hindocha 2006.i (-) **Becker 2015 (-)**		Wade 2016 (+) Kitridis 2019 (?) Skov 2017 (?) **Hindocha 2006.ii (-)** Adam 1992 (-)	**Descatha 2014 (+)**	Jerosch-Herold 2011 (?) Kitridis 2019 (?) Skov 2017 (?)	**Scheible r 2019 (-)**			Kitridis 2019 (?)		Jerosch-Herold 2011 (?) Grandizio 2017 (?) Skov 2017 (?)		Grandizio 2017 (?) Skov 2017 (?)		Jerosch-Herold 2011 (?)
Peyronie's disease	Coert 2006 (?) **Morelli 2017 (?)**	**Morelli 2017 (?)**	**Dolmans 2012 (-)**	**Morelli 2017 (?)**	Van Giffen 2006 (-) **Morelli 2017 (-)** Weckesser 1964 (?)		Bergovec 2018 (?)						Grandizio 2017 (?) Van Giffen 2006 (?)		Grandizio 2017 (?) Weckesser 1964 (?)		
PIPJ disease				Simon-Perez 2018 (-)	Stromberg 2018 (?) Simon-Perez 2018 (-) **Selles 2018 (+)** Adam 1992 (+)		Stromberg 2018 (?) Selles 2018 (?) Engstrand 2009 (?) Degreef 2009 (-)	**Scheible r 2019 (-)**		Stromberg 2018 (?)			Stromberg 2018 (?) Fei 2019 (?) Badalamente 2007 (+) O'Brien 2019 (?)*		Simon-Perez 2018 (?) Coert 2006 (+)		
Previous surgery					Adam 1992 (+) Moermans 1997 (-)		**Rodrigues 2016 (+)**								Atroshi 2015 (-)		
Pregnancy	Ferry 2013 (-)			Ferry 2013 (-)	Ferry 2013 (-)												
Quality of life					Stromberg 2018 (?) Skov 2017 (?)		Stromberg 2018 (?) Skov 2017 (?) **Engstrand 2015 (+)**			Stromberg 2018 (?)			Stromberg 2018 (?) Skov 2017 (?)		Skov 2017 (?)		
Radial disease					Abe 2004.i (+) Abe 2004.ii (+) Abe 2004.iii (+)												
Renal disease	Coert 2006 (?)																
RA			**Becker 2015 (-)**		**Hindocha 2006.ii (-)**												
Smoking	**Palmer 2014 (-)** Gudmundsson 2011 (-) Coert 2006 (?) **Descatha 2014 (-)**		Hindocha 2006.i (-) **Becker 2015 (+)**	Engstrand 2014 (?) **Broekstra 2019.i (-)***	Kitridis 2019 (?) Skov 2017 (?) Dias 2013 (-) **Hindocha 2006.ii (+)** Van Giffen 2006 (-)	**Descatha 2014 (-)**	Kitridis 2019 (?) Skov 2017 (?) **Rodrigues 2016 (-)**		Engstrand 2014 (?)		Kitridis 2019 (?)		Grandizio 2017 (?) Skov 2017 (?) Van Giffen 2006 (?) **Broekstra 2019.i (-)***		Wade 2016 (+) Grandizio 2017 (?) Skov 2017 (?)		
Thumb disease																	
Thyroid disease	Coert 2006 (?)						Bergovec 2018 (?)										
Trauma	**Marques 2002 (+)**			**Broekstra 2019.i (-)***	Skov 2017 (?) **Hindocha 2006.ii (-)** Moermans 1997 (-)		Skov 2017 (?)						Grandizio 2017 (?) Skov 2017 (?) **Broekstra 2019.i (-)***		Grandizio 2017 (?) Skov 2017 (?)		

Treatment type			Engstrand 2014 (?)	Stromberg 2018 (-) Nayar 2019 (+) Scherman 2018 (?) **Selles 2018 (+)** Dias 2013 (?)	Engstrand 2009 (+)	Stromberg 2018 (-) **Rodrigues 2016 (-)** **Engstrand 2015 (?)** Kitridis 2019 (+) Budd 2011 (-) Engstrand 2009 (+) Zyluk 2007 (+)	Engstrand 2014 (?) **Engstrand 2015 (?)**	Stromberg 2018 (-) Scherman 2018 (-)	Kitridis 2019 (-) Zyluk 2007 (-)	Stromberg 2018 (-) Engstrand 2014 (?) **Nordenskjold 2019 (+)** Nayar 2019 (+) Skov 2017 (?) Selles 2018 (+) Scherman 2018 (-) Budd 2011 (-) Engstrand 2009 (+) Fei 2019 (+) Van Giffen 2006 (?) Zyluk 2007 (+)	Wade 2016 (-) Nayar 2019 (?) Skov 2017 (?) **Rodrigues 2016 (+)**	Engstrand 2014 (?) **Engstrand 2015 (?)** Budd 2011 (-)
Tubiana stage	**Morelli 2017 (+)**	**Becker 2015 (-)**	Simon-Perez 2018 (-)	Simon-Perez 2018 (-) Van Rijssen 2012 (?) Kitridis 2019 (-) Abe 2015 (+) **Morelli 2017 (-)**		Kitridis 2019 (?)			Kitridis 2019 (?)	Abe 2015 (-) **Anwar 2007 (+)**	Simon-Perez 2018 (?)	

CTS- Carpal Tunnel Syndrome; **DIPJ**- Distal Interphalangeal Joint; **HIV**- Human Immunodeficiency Virus; **IHD**- Ischaemic Heart Disease; **IPJ-** Interphalangeal Joint; **MCPJ**- Metacarpophalangeal Joint; **RA-** Rheumatoid Arthritis.

Coloured text corresponds to the quality of studies based on the Quality In Prognosis Study (QUIPS) tool or the National Heart, Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.
(*) Non full text records identified through searching the grey literature. These were not quality appraised due to limited reporting.

Studies listed in bold are those which used multivariable analysis.

(+) evidence of association at p<0.05; (-) no evidence of association at p<0.05, (?) no quantitative analysis performed

Figure 1

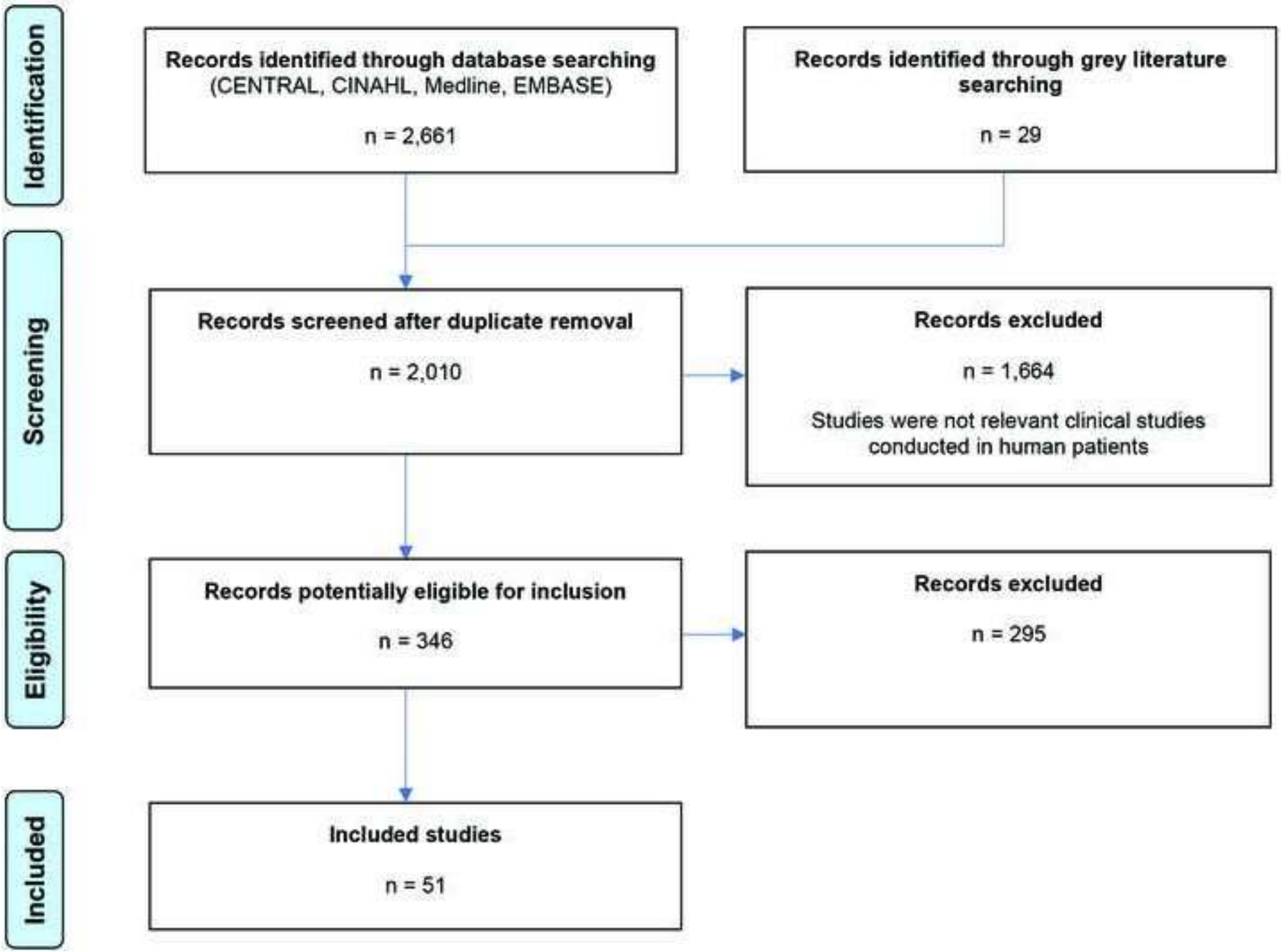

Figure 2

	Disease development	Disease progression	Disease recurrence	Self-reported disability	DASH/ qDASH	MHQ	EQ-5D	URAM	Grip strength	Joint angle correction	Complication of treatment	Range of motion
Bilateral disease	3	1	5	0	4	0	2	0	1	4	1	1
Ectopic disease	1	0	7	0	1	0	0	0	0	0	0	0
Ethnicity	3	1	2	0	0	0	0	0	0	1	1	0
Family history	6	3	15	0	5	0	2	1	0	5	4	1
Knuckle pads	4	0	4	0	1	0	0	0	0	2	2	0
Lederhosen disease	6	1	7	0	5	0	0	0	1	4	3	0
Peyronie's disease	4	1	3	0	1	0	0	0	0	2	2	0

Colors correspond to the frequency of included studies investigating association between variables:
Red: 0 studies
Orange: 1-5 studies
Yellow: 5-10 studies
Green: >10 studies