In the palm of your hand

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In the palm of your hand: prevalence, disease patterns and natural course of Dupuytren Disease

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In the palm of your hand: prevalence, disease patterns and natural course of Dupuytren Disease

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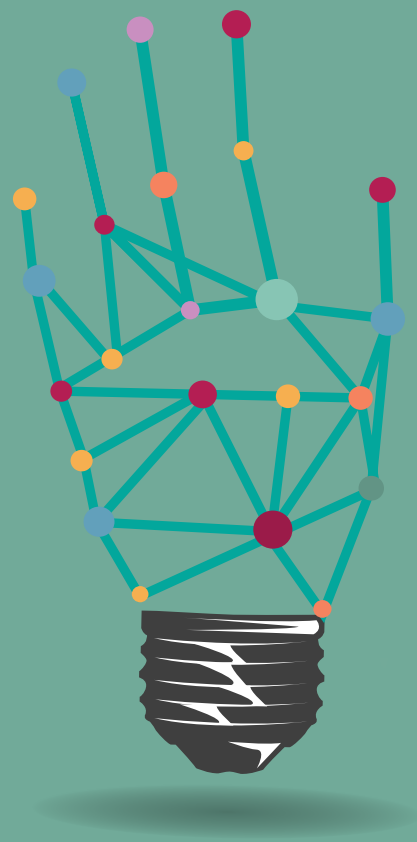

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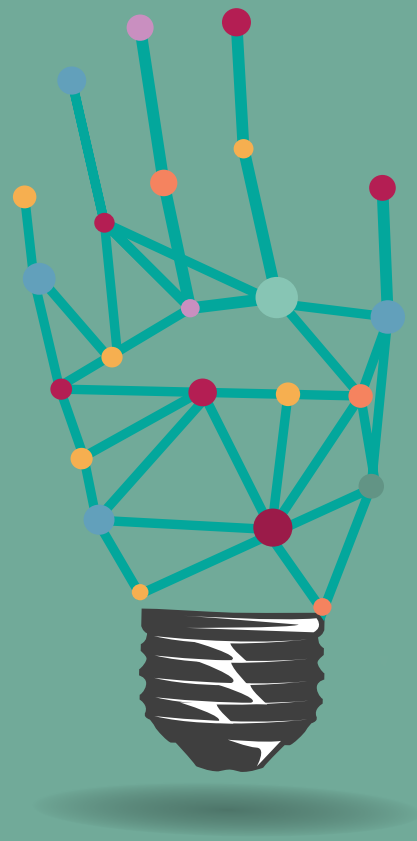

Introduction and outline of thesis

Chapter 1

Dupuytren Disease (DD) is a benign fibroproliferative disease that affects the palmar fascias of the hand and fingers. On a cellular level, the tissue that is formed contains fibroblasts, extracellular matrix proteins, and contractile myofibroblasts.[1] Clinically, this is visible as the development of nodules and cords, which may contract and can lead to extension deficits of the affected fingers (Figure 1).

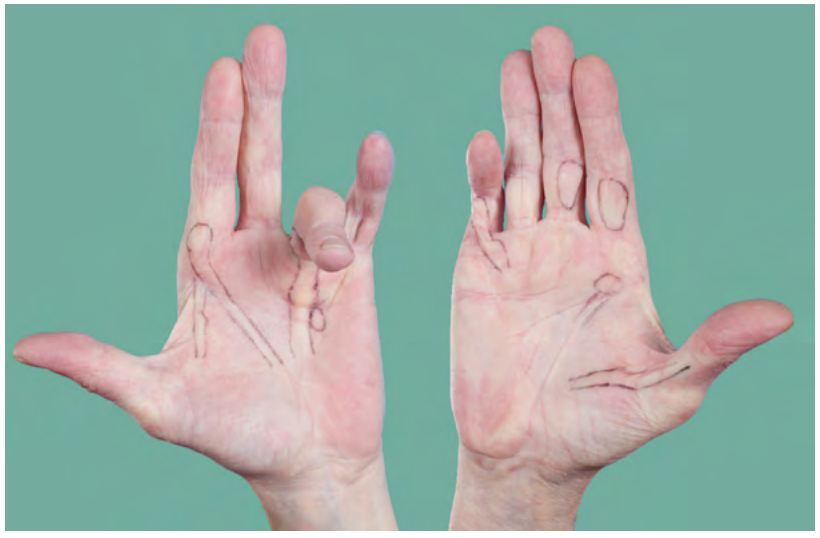

Figure 1. Recurrent Dupuytren disease in the left hand with a contracture of the ring finger and little finger. Primary disease in the right hand with a contracture of the little finger. Nodules and cords are marked with a pencil.

Diagnosis

The first manifestations of DD may be small subcutaneous irregularities in the palm. The disease becomes easier to diagnose when nodules start to appear. Nevertheless, in this stage the differential diagnosis of DD is still extensive and should include any hand condition that causes nodules or pits, such as ganglia and inclusion cysts, occupational hyperkeratosis, tenosynovitis, and giant cell tumours.[2] Cords most often affect the metacarpophalangeal (MCP) joints and/or proximal interphalangeal (PIP) joints. The disease seldom leads to contractures of the distal interphalangeal (DIP) joint, but hyperextension may develop, giving rise to a Boutonnière deformity of the affected finger.

In previous studies, several authors used their own classifications to indicate severity, which often consisted of only two or three stages.[3-7] This may be a convenient way to categorize people into different groups; however, using an accepted classification might be advantageous, because multiple categories provide a more nuanced view of severity of the disease, and results can be compared more easily.

For this purpose, different grading systems have been developed over the years. In 1936, Meyerding developed a system to assess the severity of the disease for the whole hand. This system consists of five categories, which are based on the number of affected rays and the extension deficit.[8] In the sixties, the classifications of Iselin[9] and Tubiana[10] were developed, and both classifications indicate severity per ray (Table 1). In Iselin's classification, measurements are not required for the staging in four categories. Tubiana's classification is more complex, because the severity of the disease is based on the total passive extension deficit (TPED) per finger as measured with a goniometer.[11] In addition, letters can be added to this classification to indicate the location of a lesion, for example P for palmar lesions, and D for digital lesions.[11] More recent, Abe stated that the MCP joints and PIP joints should be evaluated separately, and he developed a grading system per finger, with a focus on the severity of involvement of the PIP joint.[12]

Today, the classification of Tubiana[10] based on goniometry is most commonly used, although, the reliability of this measurement is not fully known. Several studies have investigated this for finger joint goniometry; however, these studies included participants without hand disorders.[13-15] Until now, only one study investigated the reliability of goniometry in patients with DD[16], which is remarkable, since a great value is attached to this measurement. In addition, there is no method to study disease severity in patients without an extension deficit. Therefore, it would add to the existing literature to introduce a method to study DD in patients with a mild form of the disease and to further investigate the intra- and inter-observer agreement of goniometry in patients with DD.

Table 1. Classifications of Iselin and Tubiana

Iselin		Tubiana	
Degree I	palmar nodules and small cords without signs of contracture	Stage N	nodules or cords without passive extension deficit
Degree II	contracture of the MCP joint	Stage 1	TPED of 1-45°
Degree III	contracture of the MCP and PIP joint	Stage 2	TPED of 46-90°
Degree IV	severe contracture of the MCP and the PIP with hyperextension of DIP joint	Stage 3	TPED of 91-135°
		Stage 4	TPED of >135°

MCP: metacarpophalangeal, PIP: proximal interphalangeal, DIP: distal interphalangeal, TPED: total passive extension deficit.

Prevalence

The prevalence of DD has been the subject of several studies in many different European countries, such as France, Belgium, Iceland, Norway, and the United Kingdom.[3,5,17-20] A limited number of studies has been published from other parts of the world, such as the Far East and Africa.[21,22] Data from The Netherlands is lacking. DD is known as a chronic disease of the elderly, and life expectancy will increase considerably in the coming decades. A recent report of the Central Bureau of Statistics shows that the mean life expectancy will rise to 87.1 years for males in 2060 and to 89.9 years for females. As a result of this increasing life expectancy, the retirement age will presumably be raised to 71.5 years in 2060.[23] Furthermore, it is expected that the percentage of people older than 65 years will increase from 16% in 2012 to 26% in 2040.[23] It is conceivable that this increased life expectancy will lead to an increased inflow of new patients with DD, and we will have to accommodate this inflow in order to continue providing high quality care. Therefore, it is valuable to study current prevalence rates in our region and to study the association with risk factors such as diabetes, especially with an aging population. In addition, these prevalence rates could be used to evaluate cost effectiveness of emerging treatments, such as percutaneous needle fasciotomy, radiotherapy and collagenase injection.

Published prevalence rates vary widely. Hindocha *et al*. reported a prevalence range of 0.2-56% based on 49 studies published between 1951 and 2008.[24] In contrast, a smaller range of 1-13% has also been reported.[25] Populations in which DD has been studied include inhabitants of various regions or cities, i.e., the general population[3,4,26-28], and inpatient populations from various hospitals.[29-35] Furthermore, the prevalence of DD has been studied in patients with a specific disease, such as diabetes mellitus[36-41], epilepsy[6,36,42], HIV[43,44], and rheumatoid arthritis[45]. A fourth category consists of people exposed to vibration.[20,46-48]

The prevalence rates of these previously mentioned studies are not readily comparable due to several aspects. Firstly, the sample populations are very diverse. Secondly, there may be differences in study design, and thirdly, they concern different geographic locations. The relation between these specific aspects and the prevalence of DD has never been studied before. Thus, a systematic review of the literature could provide a more accurate prevalence range of DD. This literature review should focus on the prevalence of DD in the general population and take study quality and geographic location into account. Furthermore, with an aging general population, it is interesting to perform a meta-analysis on the relation between DD and age in the general population.

Etiology

The etiology of DD has been studied extensively, but is not fully elucidated. In general, DD is more common in males, and prevalence rises with increasing age, regardless of gender.[3-5] Proposed pathophysiological mechanisms include oxidative stress and altered immune responses, which are thought to stimulate myofibroblast proliferation.[1,49] In addition, a combination of environmental and genetic factors seems to be implicated, as well as some diseases.

Risk factors and diseases that previously have been associated with DD include excessive alcohol consumption, smoking, manual work, hand trauma, diabetes mellitus, and epilepsy.[6,40,50,51] However, the specific role of each of these factors is not completely clear, and evidence is at times contradictory.

When studying the association between DD and risk factors or diseases, certain aspects regarding methodology and statistical analyses should be taken into account. Firstly, one may investigate associations in cross-sectional studies; however, it is not possible to determine a causal relationship between risk factors and DD. Such causal relationships can only be studied in a prospective cohort study. Secondly, in the statistical analyses, potential confounders that could influence the association between the supposed risk factors and DD, like age and gender, should be taken into account.

Observations from family studies and twin studies suggested that DD has a strong genetic component.[52-54] Recently, in a genome-wide association study, nine different loci on the genome were identified to have a major role in the development of DD.[55] Six of these loci comprise genes involved in the Wnt signaling pathway. This pathway influences cell proliferation and survival, and, in addition, it can change cell movement and behavior.[56] Changes in this Wnt signaling could activate cell proliferation, leading to the onset of DD.[55]

Thus, DD is a multifactorial disease in which environmental and genetic risk factors contribute in varying degrees to the onset of the disease. Further research should be conducted to study the extent that each factor contributes to the onset of DD. This will assist in fully clarifying the etiology of DD.

Disease patterns

Several authors have empirically studied the occurrence of disease patterns in fingers with DD. The results of these studies have shown that the disease is usually bilateral, and, in the case that one hand is affected, this is most often the right hand.[25,57] Furthermore, the most frequently affected rays are the ring finger and little finger on the ulnar side of the hand[4,6,7,39], and involvement of the thumb and first web space, i.e., radial involvement, is more rare.[58] Tubiana distinguished between three different types of radial involvement: (1) a mild form with a late onset by an already existing ulnar disease in the elderly patient. This form has a slow progression, and surgery is seldom necessary; (2) a moderate form, starting at age 45-50. This type is more diffuse present in both hands, and can cause contractures that might need surgical intervention; (3) a malign form, which arises at a young age in an early stage of the disease. This type is usually accompanied by ulnar contractures and can take an aggressive course.[58] It has been also been stated by others that radial involvement is associated with a severely affected ulnar side of the hand.[59,60]

Radial involvement is thought to be part of 'Dupuytren's diathesis'. The term diathesis relates to certain features of DD, which additionally include: an early onset of disease, a positive family history, bilateral hand involvement, and ectopic lesions such as Ledderhose disease and Peyronie disease.[61-63] Patients that meet the criteria of Dupuytren's diathesis are thought to experience a more aggressive course of disease with a higher recurrence rate and more disability.[62,64,65]

Empirical research has been an important first step in discovering disease patterns in DD. However, none of these studies has taken severity of the disease into account. Furthermore, firm statistical substantiation for the supposed disease patterns is lacking, and, consequently, certain findings may be questionable. For instance, the supposed association between the radial and ulnar side of the hand may be determined by the high occurrence of DD in the ring finger and little finger and could therefore be just a coincidence. Besides, it is important to realize that data in such a study is correlated, since the individual fingers belong to the hand(s) of one patient. Thus, it is relevant to conduct a study with appropriate statistical analyses, taking into consideration the variation in occurrence of DD in different fingers as well as the correlation between observations. This study could test previously stated hypotheses and clarify whether or not a correlation on the occurrence and severity of DD between fingers truly exists.

Knowledge of disease patterns could influence the decision making process with respect to treatment modalities. For example, if a strong correlation would exist between the ring finger and little finger, a surgeon might decide to treat both fingers even when treatment is indicated in only one finger. Furthermore, insight in disease patterns can be a first step towards further analysis of the role of the genotype in causing the various forms of DD.

Natural course of DD

As mentioned before, DD usually starts with small nodules in the palm of the hand, which have the capability to eventually develop into cords. The period of time in which the disease develops can differ widely between patients, and it has been described that the course of DD is characterized by periods of exacerbations and regression.[25,66,67]

Three stages has been described in the pathogenesis of DD: the proliferative stage, the involutional stage, and the residual stage.[66] In the proliferative stage, a nodule consists of young fibroblasts that are not arranged in line, and little collagen is present. In the second stage, the cells become more mature and are arranged in line. The number and size of cells decreases and the portion of collagen in the nodules increases. Nodule-cord units arise and, during this involutional stage, contraction occurs. In the last stage, which is called the residual stage, nodules disappear, and only cords are present. In this stage, the diameter of the cord varies little, and the contracture does not worsen.[66] Millesi has described similar phases and stated in addition that this process can be repeated many times, causing periods of activity and inactivity.[67]

Few studies have been conducted to investigate this disease course in patients.[68-70] These studies mainly focused on long-term progression, and therefore it is assumed that DD progresses from nodules into cords over several years. However, several drawbacks could be identified in these studies, such as crude outcome measurements[67], a retrospective design[70], and only one follow up measurement.[69,70] Consequently, the disease course is still not fully known over time, and the short term disease course should particularly receive attention.

It is important to study the course of DD in patients for various reasons. Firstly, it will contribute to our overall knowledge regarding DD. Secondly, new patients with DD are unaware of potential disabilities to expect in their future. Therefore, studying the course of DD can be used to improve patient information and

education. Thirdly, it can be used in the evaluation of the effectiveness of emerging treatments, such as radiotherapy. For instance, radiotherapy is thought to stabilize progression of the disease, especially in early-phase DD.[71,72] However, since the natural course of DD is not fully clear, it is difficult to interpret these results, because some of the stabilization might be part of the natural course of DD.

Treatment options

A flexion contracture of more than 30˚ at the MCP joint or any contracture at the PIP joint is generally thought to be an indication for treatment.[73] To this day, surgical intervention is still the most common treatment for DD, and three techniques are widely used. Firstly, in percutaneous needle fasciotomy, the cord is sectioned with an injection needle at multiple levels. Afterwards, this ray is passively extended to pull the ends of the cord apart, in order to obtain maximum release of the contracture without removal of the affected tissue.[74] Secondly, in limited fasciectomy, the diseased fascia palmaris, which includes nodules and cords, is excised via an open approach.[75] This is the most common treatment for DD in The Netherlands.[76] Thirdly, dermofasciectomy involves excision of the diseased fascia palmaris as well as removal of the overlying affected skin. A skin graft is needed to cover the evolved defect.[77] This method is used when there is a high risk of recurrence or when in recurrent disease the skin is also affected. Fourthly, emerging treatments include radiotherapy for early stage DD[72,78]; injection with collagenase *Clostridium histolyticum,* which lyses collagen and leads to disruption of contracted cords[79]; and percutaneous needle fasciotomy combined with lipofilling.[80]

Over the past years, numerous studies have been published about these different treatment options and their outcome.[72,77,79,81,82] However, it is still a challenge—especially regarding emerging treatments—to select the best patient-specific treatment and to define the most convenient moment to intervene.

To facilitate this decision, it is essential to first enlarge our knowledge about accompanying aspects of DD, such as prevalence and risk factors, disease patterns, and the natural course of DD. Until now, these aspects have received limited attention.

Aims and outline of this thesis

The main objective of this thesis is to enhance our knowledge of epidemiological aspects of DD. This general aim was subdivided into four

objectives: (1) to study prevalence rates of DD in the general population, (2) to study the reliability of measurements in DD, (3) to investigate the presence of specific disease patterns, and (4) to elucidate the short term course of the disease.

As previously mentioned, the prevalence of DD is frequently studied in different countries in Europe, except for The Netherlands. Accordingly, to address the *first objective*, we performed a prevalence study with a random sample stratified by age from the general population of Groningen. As secondary aim of this study we investigated the association between potential risk factors and prevalence of DD. The results of this study are described in **Chapter 2.** In addition, in **Chapter 3**, we show the results of a systematic review of the literature on prevalence of DD in Western countries. To address the drawbacks of previous literature reviews regarding the variety in study populations, we focused on studies conducted in the general population. Furthermore, the quality of articles was assessed in order to study whether there was an association between quality and reported prevalence. We present a prevalence range of DD in the general population of Western countries, and we report the results of a meta-analysis on the relation between prevalence and age.

In **Chapter 4,** we present the results regarding the *second objective*. The intra- and inter-observer agreement of measurement of surface area of nodules and cords was studied, as well as the reliability of finger goniometry. All measurements were performed in patients with primary DD.

With respect to the *third objective,* concerning disease patterns, we performed a cross sectional study to investigate whether there is a correlation in occurrence of DD in fingers, and if so, which patterns can be identified in the combination of affected rays. Furthermore, stated specific disease patterns in previous articles were scrutinized. Analyses were performed with a multivariate ordinal logit model, which takes into account gender, age, and severity of disease. The results are presented in **Chapter 5.**

To study the short term disease course of primary DD, which is the *fourth objective* of this thesis, we performed a prospective longitudinal study that includes over 200 patients with primary disease in at least one hand. Patients were examined every six months to obtain a reliable representation of the short term disease course; a mean of four measurements per patient was achieved. **Chapter 6** is devoted to this topic.

Chapter 7 summarizes and discusses the results of this thesis and provides future perspectives.

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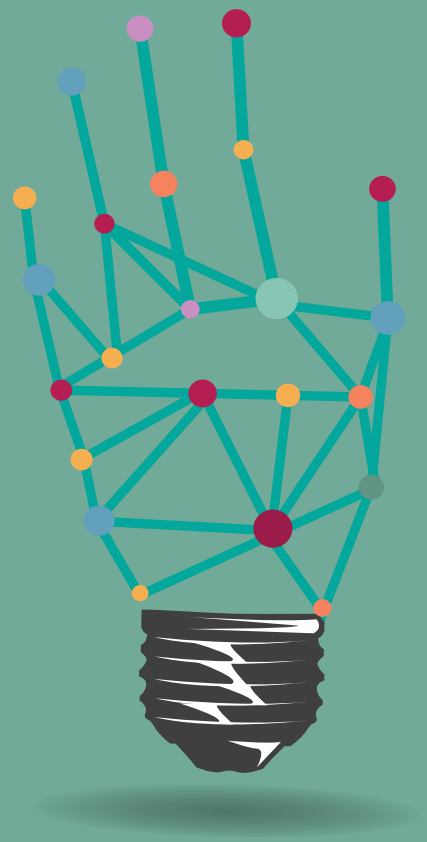

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Prevalence of Dupuytren Disease in The Netherlands

Plast Reconstr Surg. 2013;132:394-403

Chapter 2

Background

Dupuytren Disease (DD) is a fibroproliferative disease of palmar fascias of the hand. The prevalence of DD and the association with potential risk factors have been the subject of several studies, although there is a paucity of such data from The Netherlands.

Methods

To study the prevalence of DD, the authors drew a random sample of 1360 individuals, stratified by age, from the northern part of The Netherlands. Of this sample, 763 individuals aged 50 to 89 years participated in this cross-sectional study. The authors examined both hands for signs of DD, and a questionnaire was conducted to identify potential risk factors. The effects of these risk factors were investigated using logistic regression analysis. Additional analyses were performed to develop a logistic prediction model for the prevalence of DD.

Results

The prevalence of DD was 22.1%. Nodules and cords were seen in 17.9%, and flexion contractures were present in 4.2% of the study population. Prevalence increased with age, from 4.9% in participants aged 50-55 years to 52.6% among those aged 76-80 years. Males were more often affected than females; 26.4% versus 18.6% respectively (P = 0.007). Other significant risk factors were previous hand injury, excessive alcohol consumption, familial occurrence of DD, and presence of Ledderhose disease.

Conclusions

The results show a high prevalence of DD in The Netherlands, particularly the nodular form. Using the developed logistic prediction model the prevalence of DD can be estimated, based on the presence of significant risk factors.

Introduction

Dupuytren Disease (DD) is a benign fibroproliferative disease of some of the palmar fascias of the hand. This disease causes the formation of nodules which can eventually progress into cords, giving rise to flexion contractures of the affected fingers. Etiologic risk factors previously described include smoking, alcohol consumption, manual work, hand trauma, diabetes mellitus, and epilepsy.[1-4] However, the role of these factors is not fully elucidated, and evidence is at times contradictory. Observations from twin studies and family studies suggest that DD has a strong genetic component.[5-7] Recently, in a genome-wide association study, nine genes were identified to be associated with DD.[8]

The disease is particularly common in northern parts of Europe[9,10] and in countries where people of Northern European descent live. The majority of prevalence studies has been conducted in Scandinavia and in the United Kingdom. Sporadic cases have been identified in other parts of the world, such as Africa and the Far East.[11,12] The prevalence of DD has been found to vary from 0.2 to 56%,[13] indicating great heterogeneity between study populations.

Prevalence rates of Northern European countries such as The Netherlands and Germany are unknown. Since life expectancy is expected to increase considerably in the coming decades[14] and DD is a chronic disease of the elderly, it is becoming more important to improve our knowledge about current prevalence rates. Prevalence rates may be used to evaluate cost effectiveness of emerging treatments, such as percutaneous needle fasciotomy, collagenase injection, and radiotherapy.

The primary aim of this study was to determine the prevalence of DD in the general population older than 50 years in the northern part of The Netherlands. A secondary goal was to investigate the association between DD and potential risk factors.

Methods

A cross-sectional study was performed using a stratified random sample by age of 1360 inhabitants older than 50 years in Groningen, The Netherlands. The ratio of the sample size and population size in each age category was the same across age categories. The sample was drawn from the municipal administration, and our results were compared with data from the central bureau of statistics, Statistics Netherlands.[15] To conduct this study, dispensation was obtained from our institutional ethics review board. If subjects were willing to participate and signed an informed consent form, we examined both hands for signs of DD and knuckle pads. Signs of DD include tethering of the skin, nodules, cords, and finger contractures in individuals with cords. If any of these features was present, the individual was labeled as having DD. We used the classification of Iselin to assess the severity of the disease.[16] This classification consists of four categories (Figure 1):

- Degree I: palmar nodules and small cords without signs of contracture
- Degree II: contracture of the metacarpophalangeal (MCP) joint
- Degree III: contracture of the MCP and proximal interphalangeal (PIP) joint
- Degree IV: severe contracture of the MCP and the PIP joints with hyperextension

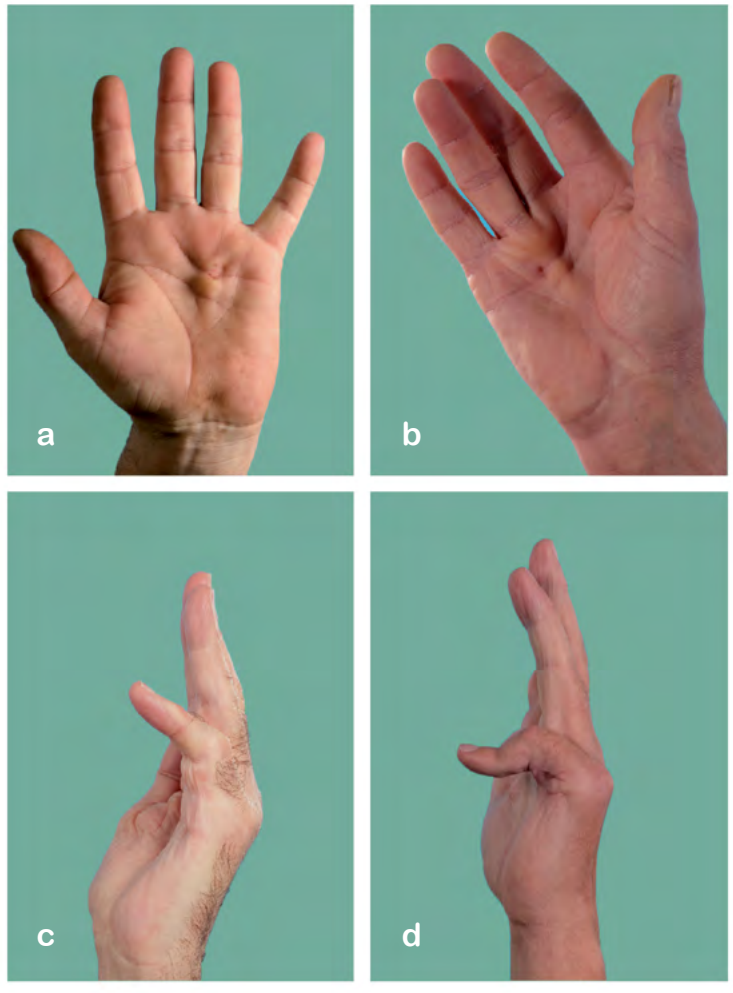

Figure 1. Iselin classification of severity of DD. (a) degree I in ring finger (b) degree II in ring finger (c) degree III in little finger (d) degree IV in little finger.

of the distal interphalangeal (DIP) joint, also known as a Boutonnière deformity. In addition to examination of the hands, we inquired about smoking habits, alcohol consumption, dexterity, whether participants had performed manual labor during a significant part of their life, and whether they had sustained hand injury in the past, including surgery. Additionally, we inquired about the presence of diabetes or epilepsy; familial occurrence of DD, defined as a relative of first degree with DD; and for presence of Ledderhose disease.

Sample size calculation

Sample size calculation was performed using a formula described by Daniel.[17] The following unknowns were imputed in the formula: P = 0.15 based on an expected prevalence of 15% as found in a previous pilot study (unpublished data), delta = 0.025 to define the length of the confidence interval, and a two-sided α of 0.05. Taking into account an estimated non-response rate of 40%, a sample size of 1360 individuals was calculated. Age stratification in eight categories was based on age distribution of the general population in Groningen, derived from the statistical yearbook 2010 of the Groningen City Council.[18] Based on the calculated sample size and the age distribution, a simulation study was conducted to investigate if the stratified sampling approach could estimate a logistic model for the prevalence of DD in age as precisely as would a random sample (results not provided).

Statistical analyses

The characteristics of the collected sample were described by medians with interquartile range (IQR) and by proportions with appropriate confidence intervals. The median age and proportion of males between the sample and nonresponders was tested using the Mann-Whitney U test and Pearson's Chi-square test, respectively. The proportion of nonresponders across age categories was tested using the Chi-square test again. The overall prevalence was calculated and categorized by disease severity. The difference in prevalence for the hands and fingers was tested with generalized estimating equations (GEE) using the cumulative logit link function, an exchangeable working correlation matrix, the robust estimator and the generalized score statistic. First, the interaction effect between hands and fingers was tested, and if not significant, the hand and finger effects were investigated separately. These effects were corrected for age categories. Odds ratios for the pairwise differences between hands and fingers

were calculated if any of the three effects (fingers, hands and interaction) would be significant at the level of α = 0.05.

In addition, the effects of possible risk factors on the prevalence of DD were investigated with logistic regression analysis. The effects of gender, diabetes, epilepsy, family history of DD, and presence of Ledderhose disease were corrected for age categories. The effects of manual labor, hand injury, alcohol consumption, smoking, and the presence of knuckle pads were corrected for gender and age categories in this analysis.

The final analyses were conducted to determine a logistic prediction model for the prevalence of DD. The risk factors with a p-value less than 0.15 from previous analysis were selected for the model, and age was taken continuous and a quadratic relation was assumed. Backward elimination using the Wald test statistic was applied at the significance level of 0.05 to develop the final model.

Results

Prevalence of Dupuytren Disease

Our stratified random sample by age included 1360 individuals. In total 763 were willing to participate; 348 males and 415 females. Population characteristics are listed in Table 1. There were no differences between the participants and nonresponders regarding gender, analyzed with Pearson's Chi-square test (P = 0.635). Age of participants ranged from 50 to 89 years, with a median age of 62 years (IQR 56 – 69). The nonresponse group had a median age of 64 years (IQR 57 – 77) and was statistically significantly older than the group of participants (Mann-Whitney U test: P < 0.001). Furthermore, nonresponse was not equally distributed over age categories (Pearson's Chi-square test: P < 0.001); in age categories younger than 70 years, more individuals were willing to participate than in the older categories. Comparison of percentages regarding smoking habits, alcohol consumption, and the presence of diabetes mellitus between our study population and the general population of The Netherlands[15] showed that there were no explicit differences between these populations (Table 2).

In total, 169 participants were affected with DD, a prevalence of 22.1% (95% CI 19.2 – 25.0). DD was more common in males than in females and prevalence increased with age (Table 3). The majority (n = 137) of the affected participants had palmar nodules without finger contractures (Iselin I). In 32 participants a contracture of one or more digits was present, a prevalence of 17.9% for nodules and 4.2 %

for contractures in our population. Primary DD was confirmed in 162 patients, and recurrent disease was much rarer; this condition was seen in only seven patients. A total of 91 patients (53.8%) had bilateral disease. In *primary* disease, 119 left hands (15.6%) and 131 right hands (17.2%) were affected. *Recurrent* disease was noted in five left hands (0.7%) and five 5 right hands (0.7%). In total, 456 rays were affected, resulting in an average of 2.7 affected rays per patient. The majority (84.9%) of the 436 *primary* affected rays had palmar nodules without contracture (Iselin I), only 49 rays (10.7%) had an Iselin score higher than I. Eight rays had been successfully operated on for DD, and in 20 rays recurrent disease was present (Figure 2).

Table 1. Population characteristics

Participants		763	-
Females (%; CI)		415	(54.4; 50.9-57.9)
Age in years (median; IQR)		62	(56-69)
Examination			
Dupuytren Disease (%; CI)		169	(22.1; 19.2-25.1)
Knuckle pads (%; CI)		116	(15.5; 12.9-18.1)
Questionnaire			
Smoking (%; CI)		184	(24.1; 21.1-27.2)
Diabetes (%; CI)		86	(11.3; 9.0-13.5)
Epilepsy (%; CI)		9	(1.2; 0.4-1.9)
Family history of DD (%; CI)		87	(11.4; 9.2-13.7)
Hand injury (%; CI)		207	(27.1; 24.0-30.3)
Manual labor (%; CI)		274	(35.9; 32.6-39.5)
Ledderhose disease (%; CI)		11	(1.4; 0.6-2.3)
Alcohol intake weekly in units (%; CI)	None	263	(34.6; 31.2-38.0)
	1-5	218	(28.7; 25.5-31.9)
	6-10	138	(18.2; 15.4-20.9)
	11-15	77	(10.1; 8.0-12.3)
	16-20	28	(3.7; 2.3-5.0)
	>20	36	(4.7; 3.2-6.2)
Dexterity (%; CI)	Left	83	(10.9; 8.7 - 13.1)
	Right	666	(87.3; 84.9 - 89.7)
	Bimanual	14	(1.8; 0.9 - 2.8)

CI: 95% confidence interval.

The difference in prevalence for the hands and fingers was tested with generalized estimating equations (GEE), excluding successfully operated rays. The results showed that there was no interaction effect between fingers and hands (P = 0.59) and that the prevalence of DD at each ray was equally distributed between both hands (P = 0.21). However, a difference between fingers was detected (P < 0.001). The most frequently affected ray was the ring finger, followed by the middle finger and little finger (Figure 3). Pairwise comparison of differences between fingers showed that prevalence of all fingers differed significantly from each other, except for the prevalence of the middle finger and little finger (P = 0.20).

Table 2. Prevalence of three study parameters in the general population of The Netherlands and our study population

		The Netherlands[a]			Study population		
Risk factor	Age category	%	SE	95% CI	%	SE	95% CI
Smoking	50-55	31.6	1.4	28.9-34.3	32.1	3.7	24.9-39.3
	56-65	26.1	1	24.1-28.1	26.9	2.5	22.0-31.7
	66-75	17.6	1.1	15.4-19.8	19.4	3.1	13.3-25.5
	> 75	10.5	1	8.5-12.5	12.4	3.0	6.5-18.3
Alcohol consumption (>20/week)	50-55	9.2	1.3	6.7-11.7	6.2	1.9	2.5-9.9
	56-65	10.1	1	8.1-12.1	4.1	1.1	1.9-6.3
	66-75	11.3	1.3	8.8-13.8	6.9	2.0	3.0-10.8
	> 75	5.5	1.1	3.3-7.7	1.7	1.2	-0.62-3.9
Diabetes	50-55	5.1	0.7	3.7-8.0	3.7	1.5	0.8-6.6
	56-65	8.0	0.6	6.8-14.0	11.6	1.8	8.1-15.1
	66-75	15.5	1	13.5-27.5	10.6	2.4	5.9-15.4
	> 75	16.1	1.2	13.7-28.1	21.5	3.7	14.2-28.8

SE: standard error, [a] data from the central bureau of statistics, Statistics Netherlands [15]

Potential risk factors for DD

The prevalence increased from 4.9% in participants aged 50-55 years to 52.6% among those aged 76-80 years (Table 3). The median age of participants with DD was higher compared to patients without the disease, 68 years (IQR 62-77.5) and 59 years (IQR 55-67) respectively (P < 0.001). DD was more common in males than in females; in total 92 males and 77 females were affected, resulting in a prevalence of 26.4% in males and 18.6% in females (logistic regression adjusted for age categories: P = 0.007; OR 1.67; 95% CI 1.15-2.24).

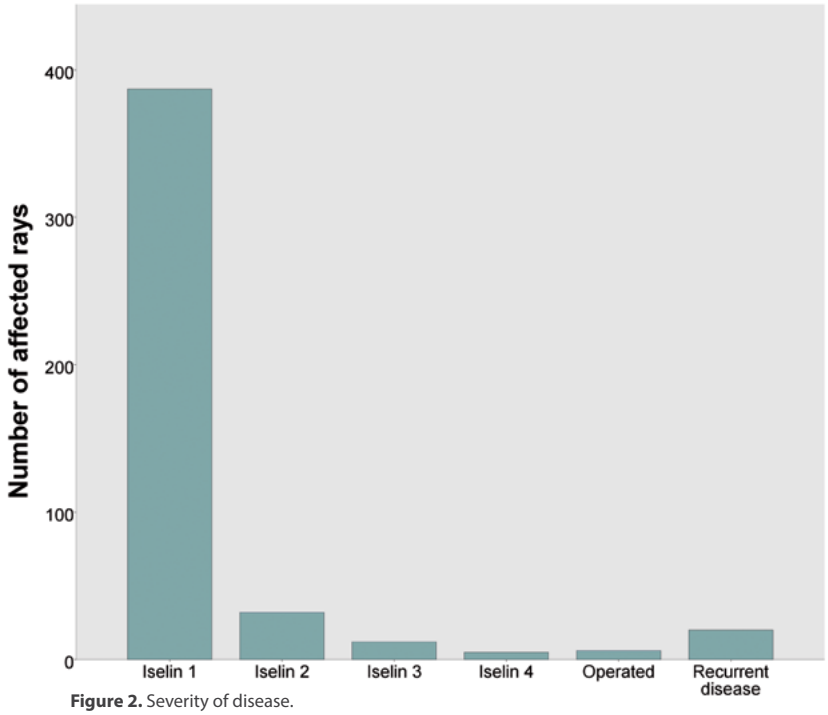

Figure 2. Severity of disease.

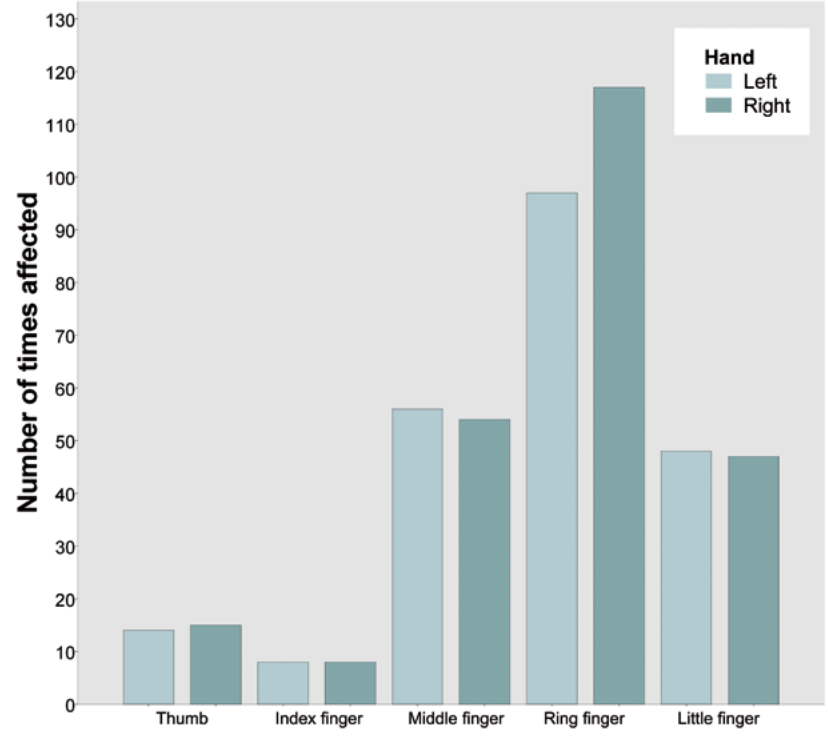

Figure 3. Number of times a certain ray was affected with DD.

Table 3. Prevalence in different age categories

Age	Total			Male			Female		
	n	DD+	DD %	n	DD+	DD %	n	DD+	DD %
50-55	162	8	4.9	72	4	5.6	90	4	4.4
56-60	174	22	12.6	78	11	14.1	96	11	11.5
61-65	146	29	19.9	66	15	22.7	80	14	17.5
66-70	99	28	28.3	49	15	30.6	50	13	26.0
71-75	61	24	39.3	29	12	41.4	32	12	37.5
76-80	57	30	52.6	24	18	75.0	33	12	36.4
81-85	31	16	51.6	14	8	57.1	17	8	47.1
86-90	33	12	36.4	16	9	56.3	17	3	17.6
Total	763	169	22.1	348	92	26.4	415	77	18.6

Number and percentages of participants with DD (DD+) in males, females and total population.

Other statistically significant risk factors for DD seen in our population were hand injury in the past, excessive alcohol consumption, familial occurrence of DD, and presence of Ledderhose disease (Table 4).

Prediction model

The final analyses were conducted to determine a logistic prediction model for the prevalence of DD. Age was entered as both a linear and quadratic effect. Table 5 shows the coefficients of the final prediction model in the logit scale after applying backward elimination. This model can be used to estimate the prevalence of DD in males and females, depending on the presence of certain risk factors (Figure 4). The model was investigated for its goodness-of-fit by adding interactions between age and age squared and the other risk factors, but none of the interactions was significant ($P > 0.175$). This goodness-of-fit test was not conducted for Ledderhose disease, because there were too few events to fit a reliable quadratic model in age for each subgroup. Furthermore, the Hosmer-Lemeshow test did not demonstrate a lack of fit of the prediction model ($P = 0.274$).

Table 4. Potential risk factors among patients with DD and the reference cohort

Risk factors	Dupuytren Disease (n = 169) (%)	Reference cohort (n = 594) (%)	Odds ratio (95% CI)	P-value
Age category (years)				
50-55	8 (4.7)	154 (25.9)	1 (NA)	
56-60	22 (13.0)	152 (25.6)	2.87 (1.20-6.45)	
61-65	29 (17.2)	117 (19.7)	4.77 (2.10-10.82)	
66-70	28 (16.6)	71 (12.0)	7.59 (3.30-17.49)	**<0.001***
71-75	24 (14.2)	37 (6.2)	12.49 (5.20-30.01)	
76-80	30 (17.8)	27 (4.5)	21.39 (8.87-51.60)	
81-85	16 (9.5)	15 (2.5)	20.53 (7.55-55.85)	
86-90	12 (7.1)	21 (3.5)	11.00 (4.03-30.02)	
Male gender†	92 (54.4)	256 (43.1)	1.67 (1.15-2.24)	**0.007***
Smoking‡	30 (17.8)	154 (25.9)	0.83 (0.52-1.33)	0.43
Alcohol consumption‡ (>15 units/week)	21 (12.4)	43 (7.3)	2.37 (1.28-4.39)	**0.006***
Diabetes mellitus†	27 (16.0)	59 (9.9)	1.17 (0.69-1.99)	0.56
Epilepsy†	5 (3.0)	4 (0.7)	4.03 (1.01-16.04)	0.05
Hand injury‡	54 (32.1)	153 (25.8)	1.56 (1.04-2.35)	**0.03***
Manual labor‡	59 (35.1)	215 (36.3)	0.91 (0.62-1.34)	0.63
Family history†	40 (23.7)	47 (7.9)	3.04(1.83-5.05)	**<0.001***
Ledderhose disease†	10 (5.9)	1 (0.2)	39.36 (4.86-318.95)	**0.001***
Knuckle pads‡	31 (19.6)	85 (14.4)	1.48 (0.90-2.44)	0.12

95% CI: 95% confidence interval. * Statistically significant difference between participants with DD and reference cohort in logistic regression analysis.
† Adjusted for age categories in logistic regression analysis.
‡ Adjusted for age categories and gender in logistic regression analysis.
Missing values patients with DD: hand injury n=1, manual labor n=1. Missing values reference cohort: alcohol consumption n=3, manual labor n=2.

Table 5. Prediction model for prevalence of DD

Risk factors	B	95% CI
Constant	-1.146	-1.4772 to -0.81476
Age	1.093	0.8183 to 1.3678
Age^2	-0.294	-0.4813 to -0.1075
Male gender	0.460	0.0676 to 0.8523
Alcohol consumption (≥15 units/week)	0.801	0.1459 to 1.4564
Family history	1.156	0.6337 to 1.6776
Ledderhose disease	3.489	1.4032 to 5.5738

95% CI: 95% confidence interval.

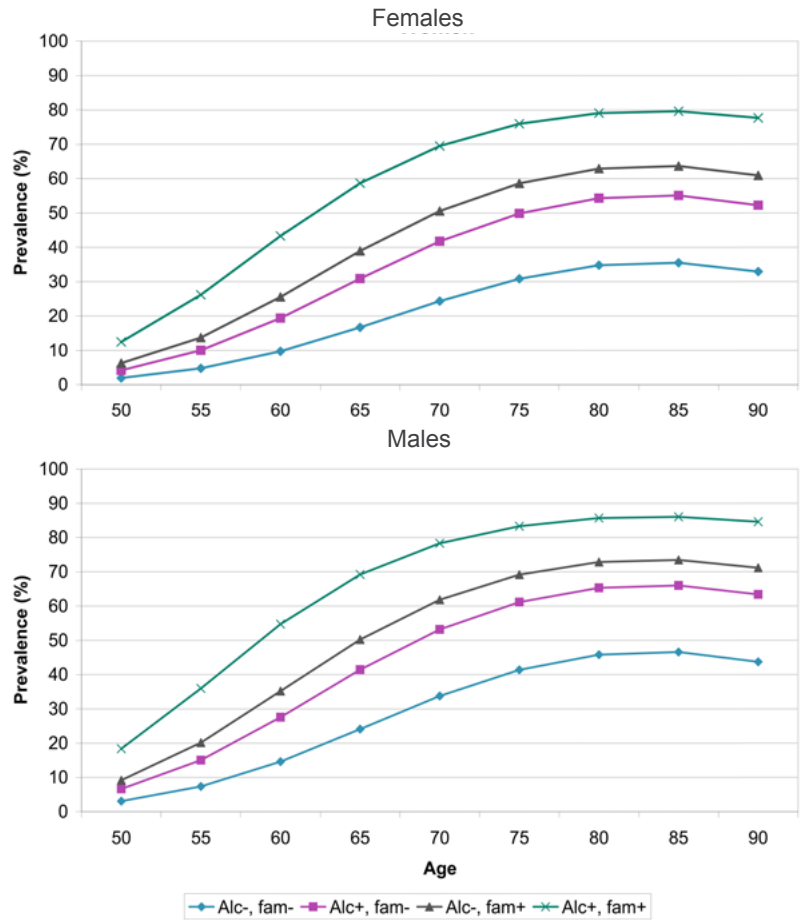

Figure 4 . Prevalence of DD in males and females. Alc- : <15 alcoholic consumptions per week, alc+: >15 alcoholic consumptions per week, fam- : no family history of DD, fam+: first degree relative with DD. Ledderhose was not included as a risk factor in this figure.

Discussion

The purpose of this study was two-fold: first, to investigate the prevalence of DD in the general population aged 50 years and older in The Netherlands; and second, to study the association between DD and potential risk factors. We conducted a cross-sectional study with a stratified random sample by age of 1360 individuals. In total 763 eventually participated. Our study revealed a prevalence of 22.1% (95% CI 19.2 – 25.0). Males were more often affected with DD than females, and prevalence increased with age from 4.9% in age category 50-55 years up to 52.6% in participants between 76 and 80 years of age.

Our findings are in agreement with results from Zerajic and Degreef, with prevalence rates of 25.4% and 31.6%, respectively, in the general population of males and females older than 50 years.[19,20] The majority of our participants only had palmar nodules; contractures were rarely seen. This is in accordance with the findings of others.[19,20] Some authors who performed studies in a nonhospital environment have found lower prevalence rates, ranging from 5.6% to 13.5%.[4,9,21-23] There are several possible explanations for this variability in prevalence, such as regional differences, since most of these prior studies were performed in Scandinavia. Second, some of the studied populations seem to be much younger than our population.[4,21,23] In the case of the 6% prevalence published by Bergenudd[9], the difference may be explained by a difference in diagnostic criteria, because they examined the hands for "Dupuytren's contracture", whereas we included the features: tethered skin, nodules, cords, and contractures.

Another cause for variability in prevalence might be a difference in experience with DD between the investigators. In the literature, an article by Noble *et al*. is often cited as an example of a discrepancy in prevalence when a physician diagnoses the disease (18%) compared with a hand surgeon (42%).[24] It is frequently suggested that the physician may have missed DD. We think that such a conclusion is unjustified, since the disease was diagnosed in two different populations that did not have similar baseline characteristics. A Danish study carried out by a nurse and a medical student also found a low prevalence of 11%.[4] However, a study in Bosnia, carried out by a junior clinician, reported a high rate of DD, suggesting that less experienced researchers may not underestimate prevalence.[19] These discrepancies complicate interpreting the importance of experience in relation to the prevalence found, especially because the prevalence figures concern different countries.

The incidence of operative intervention and recurrent disease was low in our study population. It is difficult to compare these rates with the population at large, because data about the incidence of surgical procedures for DD in the general population are not readily available. Furthermore, the majority of prevalence studies investigated merely the prevalence of current DD, and did not show data about intervention rates or recurrent disease in their study population. In 1999, Rayan suggested that there are two types of DD, namely, typical DD and atypical DD. Patients with typical DD have progressive disease which often requires surgical intervention. In contrast, patients with atypical disease have a mild form of the disease that is usually located only in the palm of the hand. This form is nonprogressive, and treatment is rarely indicated.[25] The low incidence of surgical intervention in our study population might suggest that atypical DD is common in the general population.

A secondary goal of this study was to investigate the role of potential risk factors in the development of DD. In our population, a female-to-male ratio of 1:1.2 was found. It is interesting that in several studies aimed at treatment of DD a different gender distribution was observed, ranging from 1:3.8 to 1:5.[26-28] This might suggest that the course of the disease is different in females and that treatment is less frequently performed in females than in males.

We know from previous studies that prevalence rises with age. This was supported by our results; prevalence increased strongly with rising age to a maximum prevalence of 52.6%. However, in the highest age categories a downward trend in prevalence was seen. Because of our age stratification, we believe this to be a reliable result. This finding is in agreement with some indications that patients with DD might have an increased mortality rate.[29-31] In contrast, in some studies prevalence rates continued to rise with age.[10,19,20,32-35] Therefore, the implications of this finding are difficult to interpret.

In the multivariable analyses, we adjusted for age categories because we stratified age into eight categories. In addition, in some analyses we also adjusted for gender as this might have been a confounder in certain variables, such as smoking and alcohol consumption.

In our population, there was no association between DD and diabetes in the multivariable analysis corrected for age and gender. This was in agreement with results from other studies.[1,10,19,36] Some other researchers did find a significant difference in prevalence between patients with diabetes and their control group[37-41], but it is not clear whether this effect was adjusted for age.

Several authors have tried to elucidate the association between DD and diabetes. An explanation for this association might be that microvascular changes in diabetes result in local hypoxia. This hypoxia may induce the activation of several cellular pathways, eventually resulting in formation of fibromatous tissue.[42,43] However, as mentioned, the results on this topic are contradictory.

Smoking has been associated with DD.[10,35,44] It is well known that smoking affects the peripheral circulation; this could result in peripheral hypoxia as mentioned before, and may explain the association between smoking and DD. Our findings, however, do not support this hypothesis, because smoking was not a risk

factor in our population, nor was smoking identified as a risk factor in several other studies.[9,19,45] Other previously associated risk factors that could not be linked to DD in our population are epilepsy and manual labor.

The following risk factors for DD were statistically significant in our multivariable analysis: age, male gender, hand injury in the past, excessive alcohol consumption, family history of DD, and presence of Ledderhose disease. After backward elimination, we have been able to determine a logistic prediction model for the prevalence of DD with all these risk factors except hand injury in the past. This model can be used to estimate the prevalence in males and females depending on the presence of the above-mentioned risk factors. Most parameter estimates of risk factors incorporated in the final model have a small confidence interval, but the confidence interval of Ledderhose disease is very broad because of the small number of events. Therefore, we considered the outcome of this potential risk factor less reliable and did not include this variable in the figures of our prediction model.

One of the strengths of this study was our sampling method. Because we drew a random sample stratified by age, we were able to include enough participants in each age category. Furthermore, we visited potential participants at home, which increased the willingness to participate. Nonetheless, we did not entirely reach the number of desired participants. The proportion of nonresponders was not equally distributed across age categories, and nonresponders were significantly older than the participants. This may have resulted in an underestimation of the prevalence of DD. Indeed, a weighted analysis, where the weights were selected to make the sample size in the same ratio with the population sizes, resulted in a prevalence of 23.7%. This is close to our result of 22.1%, so the imbalance in nonresponse across age categories apparently had a minimal effect on our estimate. Another strength of our study is that we compared our results with available data from the Central Bureau of Statistics (Statistics Netherlands). Because there were no explicit differences in outcome, it can be assumed that our study population accurately represents the general population in The Netherlands.

This study shows that DD—particularly, the nodular form—is common among citizens of The Netherlands aged 50 years and older. DD is highly age dependent, and is more frequently seen in males than in females. A logistic prediction model was developed to estimate the prevalence of DD based on the presence of the significant risk factors gender, age, alcohol consumption, presence of Ledderhose disease, and a positive family history of DD.

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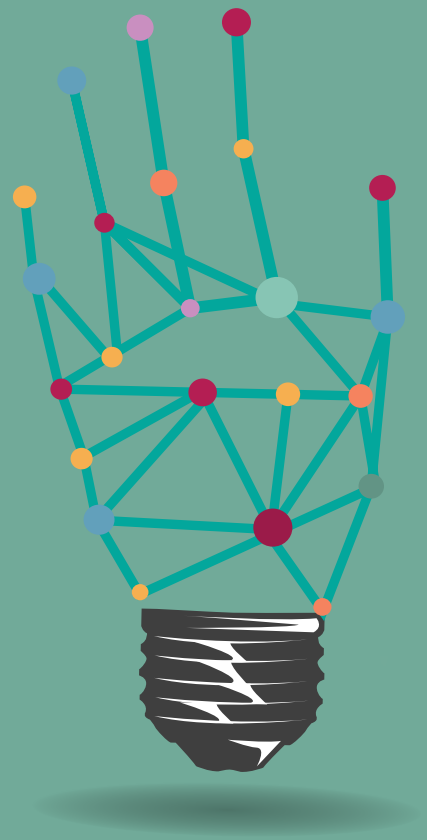

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A systematic review and meta-analysis on the prevalence of Dupuytren Disease in the general population of Western countries

Chapter 3

Background

Dupuytren Disease (DD) is a fibroproliferative disease of palmar fascia of the hand. Its prevalence has been the subject of several reviews; however, an accurate description of the prevalence range in the general population—and of the relation between age and DD—is lacking.

Methods

A systematic review was performed by searching Embase and Pubmed on database specific mesh terms; titles and abstracts were searched for "Dupuytren", "incidence", and "prevalence". Two reviewers independently assessed the articles using inclusion and exclusion criteria, and rated the included studies with a quality assessment instrument. In a meta-analysis, the median prevalence, as function of age by gender, was estimated, accompanied by 95% prediction intervals. The observed heterogeneity in prevalence was investigated with respect to study quality and geographic location.

Results

Twenty-three of 199 unique identified articles were included. Number of participants ranged from 37 to 97,537, and age ranged from 18-100 years. Prevalence varied from 0.6-31.6%. The quality of studies differed but could not explain the heterogeneity among studies. Mean prevalence was estimated 12%, 21%, and 29% at ages 55, 65, and 75 years, respectively, based on the relationship between age and prevalence determined from 10 studies.

Conclusions

The authors describe a prevalence range of DD in the general population of Western countries. Furthermore, the relationship between age and prevalence of DD is given according to gender, including 95% prediction intervals. Hereby, it is possible to determine the prevalence at a certain age for the total population, and for males and females separately.

Introduction

Dupuytren Disease (DD) is a fibroproliferative disease that affects the palmar fascia of the hand. This results in the development of nodules and cords, which eventually may contract and give rise to flexion contractures of the affected fingers. The origin of DD has been attributed to both genetic and environmental factors. The results of several family studies, and more specific twin studies, suggested that DD has a strong genetic component.[1-3] In 2011, Dolmans et al. performed a genome wide association study in which nine genes that are associated with DD were identified.[4]

Some environmental risk factors include excessive alcohol consumption, smoking, manual work and hand trauma.[5,6] In addition, several diseases, such as diabetes mellitus and epilepsy, are thought to play a role in the etiology of DD.[7-9] However, the role of these risk factors and diseases has not been fully elucidated, and the results of different studies are occasionally conflicting.

Many articles about the prevalence of DD have been published.[10-15] In these articles, there is a wide range of prevalence rates, varying from 0.2% to 56%[16,17], as reported in a previous literature review.[18] This wide range, in our opinion, may at least partly be caused by the great heterogeneity between study populations, such as healthy populations, participants with certain risk factors as well as patients with specific diseases. Suboptimal design of the included studies may also be a reason for the wide range.

Until now, no systematic review has been conducted to scrutinize the prevalence rates specifically in the general population (i.e., a healthy nonhospital population). It is assumed that life expectancy will increase considerably in the coming decades[19], and from our clinical experience we know that DD is a chronic disease of the elderly. Therefore, it will be important to enhance our knowledge about prevalence rates in the general population, and to be aware of changes in the prevalence across age. Furthermore, new treatment options have emerged, such as radiotherapy, percutaneous needle fasciotomy, and collagenase injection, and prevalence rates may be used to evaluate their cost effectiveness.

The aim of this study was to specify the prevalence range of DD in the general population (i.e., a healthy non-hospital population). This was accomplished by reviewing the literature on prevalence of DD systematically, combined with a quality assessment of the included studies. A secondary goal was to perform a meta-analysis on the relation between age and prevalence of DD.

Methods

Literature search

Our final literature search was performed on 9th of May, 2012 in the bibliographical databases PubMed and Embase, because earlier searches also in the databases "Web of Science" and "Cochrane Library" had not retrieved any additional results. PubMed was searched with the following search strategy: ("Dupuytren Contracture"[Mesh] OR Dupuytren*[TIAB]) AND ("Prevalence"[Mesh] OR prevalen*[TIAB] OR "Incidence"[Mesh] OR "incidence"[TIAB]). In Embase the following search strategy was imputed: Dupuytren*:ab,ti AND ('prevalence'/exp OR prevalen*:ab,ti OR 'incidence'/exp OR 'incidence':ab,ti) NOT [medline]/lim AND [embase]/lim.

The search was updated on 24th of January, 2013, and was supplemented by automatically weekly derived updates from PubMed until 4th of August, 2013. No limits were implemented in our search queries.

Assessment of relevant studies

Two authors (RL and DCB) independently assessed the studies in three rounds, based on predefined criteria (Textbox 1), and Cohen's kappa was calculated for each round. If in the first-round inclusion or exclusion criteria could not be assessed from the title and abstract, a full-text analysis was performed. After each round, discrepancies were discussed to reach consensus. The third author (PMNW) was consulted if no consensus could be reached.

Textbox 1. Criteria for inclusion and exclusion

Round 1. Title and abstract	**Round 2. First full text assessment**	**Round 3. Second full text assessment**
Inclusion criteria: - DD as research theme - General population as sample *Exclusion criteria:* - Case report - Case series - Review article - Subjects aged <18 years	*Inclusion criteria:* - Prevalence of DD as research theme *Exclusion criteria:* - Age is not reported - Physical examination to diagnose DD was not performed or not reported - Full text is not available	*Inclusion criteria:* - Prevalence is calculated - Data is provided to calculate prevalence *Exclusion criteria:* - Unclear how DD is diagnosed - Outcome is 'Dupuytren Contracture', not further specified - Incidence was reported instead of prevalence

DD: Dupuytren Disease

Quality assessment of included studies

We used the scoring instrument of Cho[20] to assess the quality of the studies, based on a review article on quality assessment tools for epidemiologic studies.[21] The instrument consists of 24 questions about study design, participants, methods to control bias, statistical analyses, reporting of results, and the conclusions drawn from the results.

For each question, respectively 2, 1, 0, and 0 points were awarded to the answers "yes," "partial," "no," and "not applicable", to obtain an overall quality score for each article. This was done for each question except for the question on study design; in that case, 1 to 5 points were given (1 for case reports, 2 for time series or uncontrolled experiments, 3 for cohort or case-control studies, 4 for nonrandomized control trials, and 5 for randomized control trials).[20]

Total points awarded for the 24 questions were divided by the total possible points (the sum of the maximum points for each item, excluding "not applicable" items) to generate a fraction between 0 and 1. A score of 1 represents the highest quality.[20]

All articles that were included after the second full-text round were scored with this instrument by two authors (RL and DCB) independently. The article by Lanting et al.[22] was evaluated by DCB and an independent clinical epidemiologist to avoid a conflict of interest.

Data extraction and statistical analyses

In a statistical analysis, we combined studies that provided information on prevalence and sample sizes for different age categories in a total population, or in males and females separately. The aim of this meta-analysis was to determine a population-averaged relationship between age and DD, and to study possible heterogeneity in this relationship between studies. The midpoints of the age categories were used in a generalized linear mixed model. The form of the age-prevalence relationship was selected equal to an asymmetric logistic function with a random intercept for study to address possible heterogeneity. This model was applied to the data of males and females simultaneously with a random intercept for males and females that was correlated. A simpler model with only one random intercept was applied to the totals of males and females, since some studies did not provide data separately by gender. From the estimated models and the random effects, a range of age based predicted prevalences was estimated (i.e. 95% prediction intervals). In addition, in case heterogeneity was present, it was investigated whether the overall quality score, the quality of study design or geographic location affects the heterogeneity.

In some of the studies, the prevalence was determined in patients with a specific disease, and in a control group. If that was the case, only the data from the control group were used. The exact 95% confidence intervals for the overall proportion of DD were calculated using the F-distribution.[23]

Results

Results of literature search and assessment of relevant studies

The search resulted in 212 articles. After excluding duplicates and critical appraisal of the studies by predefined criteria (Textbox 1), 23 studies were included (Figure 1). Two main reasons led to exclusion: first, the prevalence of DD was not determined, and second, the study population was not a general population. As a consequence also all non-English papers were excluded. To quantify the decisions

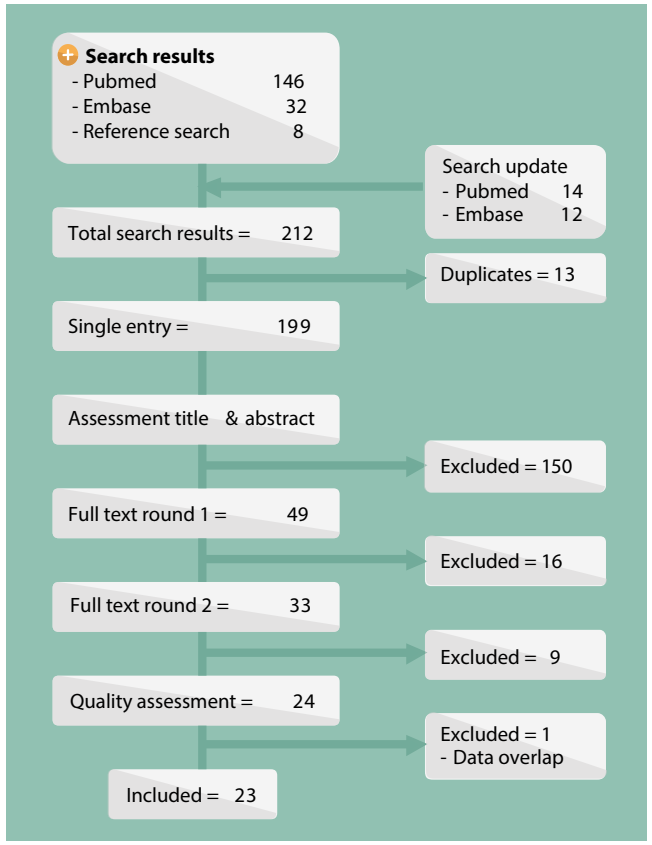

Figure 1. Flowchart of study selection procedure.

in the selection process, we performed a Cohen's kappa analysis for each round of assessment: title and abstract (κ = 0.623, P < 0.001); full-text round 1 (κ = 0.449, P = 0.001); and full-text round 2 (κ = 0.528, P = 0.001).

As shown in Table 1, articles were published between 1972 and 2013. In some studies, only data from the control group were used (noted as CG in Table 1). Several times these control groups were chosen from a population that sustained hand pathology.[24-26] In two studies it was explicitly noted that the control group did not suffer from hand pathology.[27,28]

The total number of participants in the included studies ranged from 37 to 97,537, and in seven of these studies only males participated.[29-35] Age ranged from 18 to 100 years, with an average above 50 years in 12 studies. In six studies age was only reported in categories, without absolute number of participants in each category, so it was not possible to calculate a mean age (CAT in Table 1).[26,27,34,36-38]

The lowest prevalence found was 0.6%, compared with 31.6% as highest prevalence over all age groups.[12,39] In two studies, DD was diagnosed in a different fashion compared with the other studies. Descatha et al. did not include palmar thickening as sign of DD, and Lucas et al. excluded the thumb from examination.[32,33] The quality score is depicted in the last column of Table 1; this score ranged from 0.23 to 0.80.

Results of quality assessment

Table 2 shows in detail the results of the quality assessment per question, and Table 3 shows the score on the different questions per study. Question 2 is an open question that does not contribute to the final score.

The majority of studies reported the study question only partially. In 13% of the studies the inclusion and exclusion criteria were completely explained, whereas in 61% these criteria were not depicted at all. In almost 80% of the articles, the subjects were not randomly selected from the target population, or this was not reported. Only one of the 23 studies reported a sample size justification.[22]

Regarding the statistical analyses, almost a quarter of the papers did not report which analyses were performed, and in only 52%, the performed analyses were fully appropriate to answer the research question. The effect of confounders was most frequently corrected in the statistical analyses, and not beforehand in the study design.

In 70% the conclusion of the study was fully supported by the findings. However, in one study the results point to a contrary conclusion than reported.[26]

Table 1. Details of included studies

Authors	Year	Population	N	Gender	Age			Prevalence (95%CI)	Quality score
					Mean	SD	Range		
Arafa[36]	1984	Patients of fracture clinic (CG)	555	F & M	CAT			16.0 [13.1 ; 19.4]	0.46
Ardic[24]	2003	Non-diabetic patients of department of physical medicine and rehabilitation (division rheumatology) (CG)	37	F & M	55.7	11.5	30-79	2.7 [1.0 ; 14.2]	0.44
Attali[40]	1987	Patients of gastroenterology unit without alcoholism or chronic liver disease (CG)	174	F & M	58.9	22.7		12.5 [8.1 ; 18.5]	0.49
Aydeniz[41]	2008	Non-diabetic patients of public health clinic (CG)	101	F & M	60.1	7.6		4.0 [1.1 ; 9.8]	0.51
Bennettt[29]	1982	Workers PVC manufacturing plant not involved with bagging or packing (CG)	84	M	40.1			1.19 [0.0 ; 6.5]	0.46
Burke[30]	2007	Miners seeking compensation for Hand-Arm Vibration Syndrome	97537	M	53.5			8.13 [8.0 ; 8.30]	0.62
Carson[31]	1993	Ex-military service pensioners in the Royal Hospital Chelsea	400	M	75.9		65-99	13.8 [10.5 ; 17.5]	0.38
Degreef[12]	2010	Visitors of markets in Flanders, Belgium	500	F & M	70.4		50-100	31.6 [27.5 ; 35.9]	0.46
Descatha[32]	2012	Employees in private sector in Pays de la Loire, France	2161	M	38.5		20-59	1.25 [0.8 ; 1.8]	0.66
Eadington[13]	1989	Normotensive, non-diabetic subjects, selected from inpatients, outpatients and hospital staff members (CG)	150	F & M	51.2	17.4		18.0 [12.2 ; 25.1]	0.64
Finsen[37]	2002	Residents of rural municipalities in Norway	456	F & M	CAT		50-80+	7.5 [5.05 ; 9.87]	0.51
Gudmunds-son[15]	2000	Residents of Reykjavik and adjacent communes, Iceland	2165	F & M	57.5		45-94	13.3 [11.9 ; 14.8]	0.56
Lanting[22]	2013	Residents of Groningen, The Netherlands	763	F & M	62.0*		56-69**	22.1 [19.3 ; 25.3]	0.80
Lennox[27]	1993	Patients on geriatric ward, not admitted for hand pathology	200	F & M	CAT			30.0 [23.7 ; 36.9]	0.37
Lucas[33]	2008	Civil servants of Pays de la Loire and Brittany, France	2406	M	45.3	7.6		8.8 [7.7 ; 10.0]	0.64
Mikkelsen[42]	1972	Residents of Haugesund, Norway	15950	F & M	45.0		16-99	5.6 [5.3 ; 6.0]	0.46
Noble[26]	1992	Patients of fracture clinic (CG)	100	F & M	CAT			8.0 [3.5 ; 15.2]	0.36
Noble[25]	1984	Patients of fracture clinic (CG)	150	F & M	57.4			18.0 [12.2 ; 25.1]	0.28
Pal[28]	1987	Non-diabetic subjects without musculoskeletal complaints (CG)	75	F & M	44.0*		18-76	9.0 [3.8 ; 18.3]	0.49
Rafter[34]	1980	Inpatients in acute medical and surgical wards	403	M	CAT			17.1 [13.6 ; 21.2]	0.23
Ravid[39]	1977	Non-diabetic patients of different departments of medicine (CG)	1396	F & M	52.0		19-86	0.6 [0.3 ; 1.2]	0.49
Thomas[35]	1992	Patients admitted to general surgical ward (CG)	150	M	64.1		50-85	10.7 [6.2 ; 16.7]	0.46
Zerajic[38]	2004	Visitors of public places in both urban and rural areas of Bosnia Herzegovina	1207	F & M	CAT			25.4 [23.0 ; 28.0]	0.59

CG: control group, N: number of participants, SD: standard deviation, CI: confidence interval, CAT: age reported only in categories, * median ** inter quartile range.

Explorative analysis

The generalized linear mixed model indicated substantial heterogeneity between studies, meaning that prevalence varies between studies. It was explored whether the overall quality score and the subscore on methodology (questions 1, 4, 7-9, 14-17, 19 in Table 3) were related to the heterogeneity. The goal of this analysis was to check whether selecting studies on quality would narrow the prevalence range substantially. The distance of each study to the median profile in Figure 2 was plotted against the variables of interest. No clear pattern was observed for the quality scores or the subscores; both low- and high-quality studies appear on both sides of the median prevalence for all levels. This indicates that the quality of a study did not explain the variation in prevalence; thus, no studies were excluded for further analyses based on quality score. Furthermore, we investigated whether the heterogeneity was explained by the geographic location (i.e., whether the relative difference of a study to the median age-related prevalence fits with an order in geographic location), but no clear trend was visible. For example, the prevalence found by both Bennett[29] and Burke[30] was below the median age-related prevalence curve and the prevalence found by Arafa[36] was above this median, whereas they all came from the same geographic location: England. In contrast, prevalences in the Nordic countries all seem to be below the median curve. Instead of trying to understand the influence of geographic location, we calculated, based on our model, 95% prediction limits (the outer limits in Figure 2). These limits indicate the range of expected true age-related prevalence of DD in observed and unobserved geographic locations in Western countries.

Relation between age and prevalence of DD

A combined analysis of 10 studies[12,15,22,25-27,36-38,42] representing information on prevalences in different age groups showed an overall relationship that is visualized in the upper graph of Figure 2. In the middle and lower graph of Figure 2, this relationship is shown respectively for females (8 studies[12,15,22,27,36-38,42]) and males (11 studies[12,15,22,27,29,30,32,36-38,42]). The prevalence is shown as well as the 95% confidence intervals (inner dotted lines), taking into account the heterogeneity between studies. Furthermore, a 95% prediction interval is presented (outer dashed lines), which makes it possible to predict the prevalence at a certain age in a healthy nonhospital population. For instance, the overall prevalence of DD is estimated 12% in those aged 55 years, and 29% in those aged 75 years. The prediction band

can be used to estimate the a priori prevalence in a random sample at different ages and geographic locations. Clearly, the prevalence increases with rising age. Furthermore, the graphs show that the prevalence of DD is higher in males than in females. In addition, the age of onset is lower in males compared with the age of onset in females.

Table 2. Quality assessment of included studies per question

Answer:		Yes		Partial		No		NA	
	Question	n	%	n	%	n	%	n	%
1	Study design †								
2	What was the study question? ‡								
3	Was the study question sufficiently described?	5	22%	15	65%	3	13%	0	0%
4	Was the study design appropriate to answer the study question?	21	91%	2	9%	0	0%	0	0%
5	Were both inclusion and exclusion criteria specified	3	13%	6	26%	14	61%	0	0%
6	For case studies only: Were patient characteristics adequately reported?*	0	0%	0	0%	0	0%	23	100%
7	Were subjects appropriate to the study question?	19	83%	4	17%	0	0%	0	0%
8	Were control subjects appropriate?	12	52%	6	26%	5	22%	0	0%
9	Were subjects randomly selected from the target population?	5	22%	0	0%	18	78%	0	0%
10	If subjects were randomly selected, was the method of random selection sufficiently well described?	1	4%	1	4%	3	13%	18	78%
11	If subjects were randomly allocated to treatment groups, was method of random allocation sufficiently described?**	0	0%	0	0%	0	0%	23	100%
12	If blinding of investigators was possible, was it reported?**	0	0%	0	0%	0	0%	23	100%
13	If blinding of subjects to intervention was possible, was it reported?**	0	0%	0	0%	0	0%	23	100%
14	Was measurement bias accounted for by other methods than blinding?	6	26%	11	48%	6	26%	0	0%
15	Were known confounders accounted for by study design?	5	22%	3	13%	13	57%	2	9%
16	Were known confounders accounted for by analysis?	9	39%	5	22%	7	30%	2	9%
17	Was there a sample size justification before the study?	1	4%	0	0%	22	96%	0	0%
18	Were post hoc power calculations or confidence intervals reported for statistical non significant results?	4	17%	4	17%	15	65%	0	0%
19	Were statistical analyses appropriate?	12	52%	5	22%	6	26%	0	0%
20	Were the statistical tests stated?	6	26%	12	52%	5	22%	0	0%
21	Were exact values or confidence intervals reported for each test?	5	22%	13	57%	5	22%	0	0%
22	Were attrition of subjects and reason for attrition recorded?	4	17%	3	13%	16	70%	0	0%
23	For those subjects who completed the study; were results completely reported?	15	65%	7	30%	1	4%	0	0%
24	Do the findings support the conclusions?	16	70%	6	26%	1	4%	0	0%

n: number of studies, %: percentage, NA: not applicable, † See Table 3, ‡ Open question which does not contribute to final score, * Case studies were not included, so question 6 was not applicable for each of the included articles,
** Questions were not applicable, because this concerns intervention studies.

Investigating the goodness-of-fit of the estimated models, the R^2 was calculated between the observed numbers of DD, and the predicted numbers of DD from the model. For males the R^2 was estimated at 99.5%; for females the R^2 was equal to 93.0%; and for males and females together the R^2 was 97.5%, which demonstrates a good fit of the generalized linear mixed model. This indicates that the models in Figure 2 are able to predict new observations with high certainty. The high goodness of fit may not seem in line with the observed outliers outside the prediction limits in Figure 2. However, several of these outliers were based on small number of subjects (Table 4). For instance, when only one subject is observed in an age category, the prevalence can only be estimated at either 100% or 0% depending on the outcome of DD. The prediction intervals hold true for relative large sample sizes.

Table 4. Studies outside prediction intervals

Population	Age cat.	Author	n DD	n total	% DD	95% PI
Total	<30	Arafa[36]	1	34	2.9	0.02–0.6
	30-34	Mikkelsen[42]	1	1043	0.1	0.1–2.9
	30-39	Arafa[36]	4	47	8.5	0.2–4.4
	30-39	Noble [25]	1	5	20.0	0.2–4.4
	50-59	Finsen[37]	2	103	1.9	2.5–27.5
	61-65	Degreef[12]	32	86	37.2	5.3–37.2
	75-79	Zerajic[38]	43	72	59.7	12.3–49.4
	76-80	Lanting[22]	30	57	52.6	12.8–50.2
	>80	Finsen[37]	0	24	0.0	16.8–54.4
	95-99	Mikkelsen[42]	0	3	0.0	24.3–61.0
Males	<30	Descatha[32]	0	491	0.0	0.1–4.2
	55-64	Bennett[29]	0	9	0.0	2.8–42.0
	75-79	Zerajic[38]	30	40	75.0	7.6–53.8
	76-80	Lanting[22]	18	24	75.0	8.0–54.3
	>80	Finsen[37]	0	7	0.0	10.4–57.5
	80+	Zerajic[38]	24	40	60.0	9.4–56.4
	81-85	Lanting[22]	8	14	57.1	9.8–56.8
	>90	Lennox[27]	4	6	66.7	14.5–61.6
	90-94	Mikkelsen[42]	1	1	100.0†	13. 5–60.7
	95-99	Burke[30]	0	1	0.0	15.6–62.5
	95-99	Mikkelsen[42]	0	1	0.0	15.6–62.5
Females	81-85	Lanting[22]	8	17	47.1	0.3–46.8

Age cat: age category, n DD: participants with DD, n total: total participants, % DD: percentage of participants with DD, 95% PI: 95% prediction interval, † Outlier not visible in Figure 2 (Y-axis ranges from 0-80%).

Table 3. Quality assessment of included studies per study

Author	Questions†																						Total	Max. points	Score
	1	2‡	3	4	5	6*	7	8	9	10	11**	12**	13**	14	15	16	17	18	19	20	21	22	23	24			
Arafa[36]	2	0	1	0	NA	2	1	2	0	NA	NA	NA	2	2	1	0	0	0	1	1	0	2	2	2	19	41	0.46
Ardic[24]	2	1	2	0	NA	2	0	2	0	NA	NA	NA	1	1	0	2	0	0	1	1	0	2	2	2	18	41	0.44
Attali[40]	2	1	2	0	NA	2	2	2	0	NA	NA	NA	0	0	0	2	0	0	2	1	1	1	0	2	19	39	0.49
Aydeniz[41]	2	1	2	1	NA	2	2	2	0	NA	NA	NA	0	2	2	0	0	0	1	1	1	1	0	1	20	39	0.51
Bennett[29]	2	1	2	0	NA	2	2	2	0	NA	NA	NA	2	1	0	2	0	0	1	1	0	2	2	2	18	39	0.46
Burke[30]	2	2	2	0	NA	2	2	2	0	NA	NA	NA	1	1	0	2	0	0	2	2	2	1	2	2	24	39	0.62
Carson[31]	2	0	2	0	NA	2	2	2	0	NA	NA	NA	1	1	0	1	0	0	1	1	1	0	2	2	15	39	0.38
Degreef[12]	2	1	2	2	NA	2	2	2	0	NA	NA	NA	2	2	0	0	0	0	1	1	1	0	2	2	18	39	0.46
Descatha[32]	2	1	2	2	NA	2	2	2	0	0	NA	NA	1	1	0	2	0	0	2	1	1	1	2	2	27	41	0.66
Eadington[13]	2	2	2	2	NA	2	1	0	NA	NA	NA	NA	1	0	1	2	0	1	2	2	1	1	2	1	25	39	0.64
Finsen[37]	2	1	2	1	NA	2	0	0	NA	NA	NA	NA	0	0	1	0	0	1	2	2	1	2	1	1	20	39	0.51
Gudmundsson[15]	3	1	2	0	NA	2	2	2	1	NA	NA	NA	1	1	0	2	0	0	1	1	0	1	1	1	23	41	0.56
Lanting[22]	2	2	2	0	NA	2	2	2	2	NA	NA	NA	1	2	2	2	0	2	2	2	1	0	2	2	33	41	0.80
Lennox [27]	2	1	2	0	NA	1	0	0	NA	NA	NA	NA	1	1	NA	NA	0	0	1	1	1	0	1	2	13	37	0.37
Lucas[33]	2	1	2	1	NA	1	2	0	NA	NA	NA	NA	1	1	NA	NA	0	0	2	2	1	2	1	1	25	39	0.64
Mikkelsen[42]	2	1	2	1	NA	2	0	0	NA	NA	NA	NA	2	2	NA	NA	0	0	2	2	2	1	2	2	16	35	0.46
Noble [25]	2	0	2	0	NA	2	1	0	NA	NA	NA	NA	0	0	2	0	0	0	0	1	0	0	0	1	11	39	0.28
Noble[26]	2	1	2	0	NA	1	1	0	NA	NA	NA	NA	0	0	1	0	0	0	2	1	1	1	2	0	14	39	0.36
Pal[28]	2	2	2	2	NA	2	2	0	NA	NA	NA	NA	2	2	0	0	0	0	1	1	1	1	1	0	19	39	0.49
Rafter[34]	2	1	1	0	NA	1	2	0	NA	NA	NA	NA	2	0	0	0	0	0	0	1	1	0	1	1	9	39	0.23
Ravid[39]	2	2	2	0	NA	2	1	0	NA	NA	NA	NA	0	0	2	1	0	0	2	1	0	0	2	2	19	39	0.49
Thomas[35]	2	1	2	0	NA	2	1	0	NA	NA	NA	NA	1	1	0	0	0	0	2	1	0	1	2	2	18	39	0.46
Zerajic[38]	2	1	2	1	NA	2	0	0	NA	NA	NA	NA	NA	2	1	0	0	1	2	2	1	2	2	2	23	39	0.59

† Questions: 1: Study design, 2‡: Research question, 3: Study question sufficiently described, 4: Study design appropriate to answer study question, 5: Inclusion and exclusion criteria specified, 6*: Case studies: patient characteristics adequately reported (not shown), 7: Subjects appropriate to study question, 8: Control subjects appropriate, 9: Random selection of subjects, 10: Method of random selection sufficiently well described, 11**: Random allocation to treatment group sufficiently described, 12**: Blinding of investigators to intervention reported, 13**: Blinding of subjects to intervention reported, 14: Measurement bias accounted for by methods other than blinding, 15: Known confounders accounted for by study design, 16: Known confounders accounted for by analysis, 17: Sample size justification, 18: Post hoc power calculations or confidence intervals reported for statistically non significant results, 19: Appropriate statistical analyses, 20: Statement of statistical tests, 21: Exact values of confidence intervals reported for each test, 22: Reporting of attrition of subjects who completed the study, 24: Findings support the conclusion.
Question 1 was scored 3 (cohort design) or 2 (cross-sectional design), other questions were scored 2 (yes), 1 (partial), 0 (no), NA (not applicable). The score was calculated by dividing the total points by the maximum possible points. A higher score represents a higher quality.
‡ Open question which does not contribute to the final score (not shown) * Case studies were not included, so question 6 was not applicable for each of the included articles and therefore not shown.
** Questions were not applicable, because this concerns intervention studies and therefore not shown.

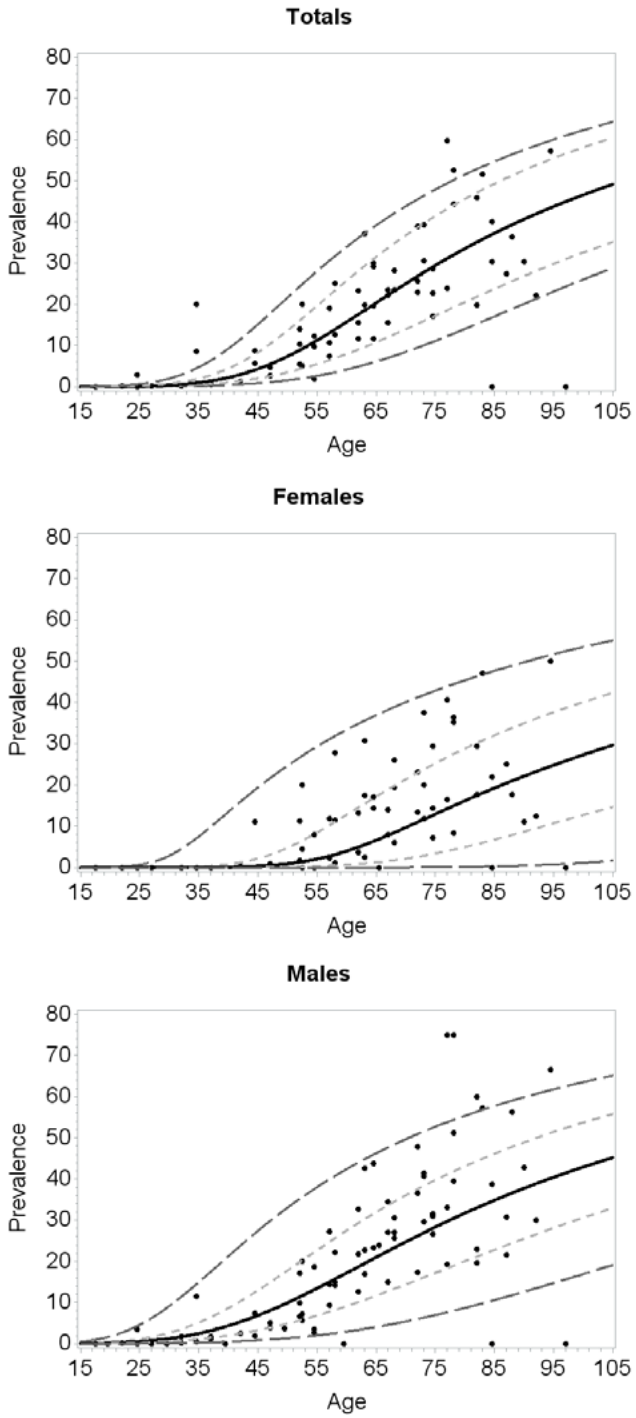

Figure 2. Relationship between age and DD. Upper graph: totals, middle graph: females, lower graph: males. Bold line: estimated prevalence, dotted line: 95% confidence interval, dashed line: 95% prediction interval, dots: individual prevalence estimates used in the analysis.

Discussion

DD is a hand disorder, which is often progressive and eventually can cause contractures of the affected fingers. The reported prevalence rates vary widely in the literature. Therefore, the primary goal of this systematic review was to come to a more accurate distribution of the prevalence of DD in the general population. A secondary goal was to perform a meta-analysis on the relation between prevalence of DD and age.

To our knowledge, this systematic review is the first of its kind. First, it focuses on prevalence rates specifically in the general population of Western countries (i.e., a healthy nonhospital population), excluding specific patient groups. Second, the quality of the studies was assessed critically. Previous reviews about prevalence of DD concern different kinds of populations, such as manual workers[43], rock climbers[44,45], and a mixture of healthy participants and patients with a specific disease.[18] Furthermore, geographic location was studied and we performed a thorough meta-analysis on the relationship between age and DD.

Our English search strategy was performed in English databases, so we might have missed relevant articles in foreign languages. However, despite this limitation, several articles in foreign languages, such as German, French and Italian, entered the full-text analysis. The kappa for each round of assessment was moderate, emphasizing the necessity of discussing the assessment with multiple authors.
After the full-text analysis, 23 studies were included, with a number of participants ranging from 37 to 97,537 in the age range of 18 to 100 years. Prevalence in these studies varied from 0.6% to 31.6%, which is a smaller range than previously published.[18]

During the quality assessment we came across a number of noteworthy points. First, only few studies reported that they applied sampling to select their participants.[15,22,24,32,36] However, three of these studies did not describe the method of sampling.[24,32,36] If participants are not selected randomly, the risk of selection bias increases, which makes extrapolation of data from these studies difficult. Second, only one study reported a sample size justification.[22] In an observational study, the accuracy of the estimates (i.e., the prevalence), depends on sample size.[46] If a sample size is not calculated beforehand, the results of the study might be less precise than intended. Finally, in only a quarter of the studies were the statistical tests stated fully, and in 52% the analyses were completely appropriate. To enlarge the reproducibility of the results, it is essential that such information is documented

properly. More importantly, to ensure that correct conclusions can be drawn, it is crucial that appropriate analyses are performed.

To narrow the prevalence range, we intended to select studies for further analysis, based on their quality. The final overall quality score differed from 0.23 to 0.80. However, in the explorative analysis, no relation was found between this quality score and the reported prevalence. This is in accordance with the findings in a meta-analysis in which the meta-odds ratio for manual work and vibration exposure of all studies was similar to the meta-odds ratio of only high quality studies.[43]

Several articles have been published about the difficulties using an overall score to assess the quality of a study.[47-49] With an overall quality score it is hard to discriminate between poor reporting and poor methodology of the study. Thus, it is advised that articles be evaluated based on key components rather than an overall score.[21,47,50] Therefore, we analyzed the relation between a high score on methodology and the prevalence of DD. Still, no link was found, so we assumed that the current spread in prevalence was based not on a difference in quality of the studies, but on heterogeneity of the study populations.

We aimed to include studies with participants from a general population. However, we ended with studies that did not provide information about race and that originated mainly from Europe. Nonetheless, the biogeographic regions in Europe differ from Arctic to Mediterranean. Based on our model, we suppose that the prevalence in different geographic locations lies within the prediction interval of Figure 2, but more thorough analyses with additional variables are necessary to clarify and understand the geographic influence on the prevalence of DD.

As mentioned in the Results section, two studies diagnosed DD differently than other studies.[32,33] Although this did not change our prevalence range substantially, differences in diagnosing DD complicate the comparison of results. Preferably, all stages of DD in all rays are taken into account, for example, by using the classification of Iselin or Tubiana.[51,52] Furthermore, there were differences in reporting age; six studies reported age in categories, without giving the actual range.[26,27,34,36-38] The discrepancies in reporting age also impede comparison of prevalence rates of different studies. Fortunately, we have been able to use data of different age categories in our meta-analysis.

It is well recognized that prevalence of DD increases with rising age; however, until now, a thorough analysis on this relationship was lacking. In our meta-analysis, we investigated this relationship by using all studies that provided information on prevalence in different age categories. We presented the relationship between age and DD, including 95% confidence intervals and 95% prediction intervals. The graphs can be used to determine a common estimate for the prevalence of DD at different ages, both for the total population as well as for males and females separately. Nowadays, still little is known about the prevalence of DD in younger people, because in most studies age older than 50 years was one of the inclusion criteria. However, the relationship between age and prevalence presented in this paper already provides a first indication for prevalence at a younger age.

Conclusion

The prevalence of DD in the general population of Western countries ranges from 0.6% to 31.6%. With the results of our meta-analysis, we have been able to present the relationship between prevalence of DD and age, including confidence intervals and prediction intervals. With the presented graphs it is possible to determine the prevalence at a certain age for the total general population of Western countries, and for men and women separately.

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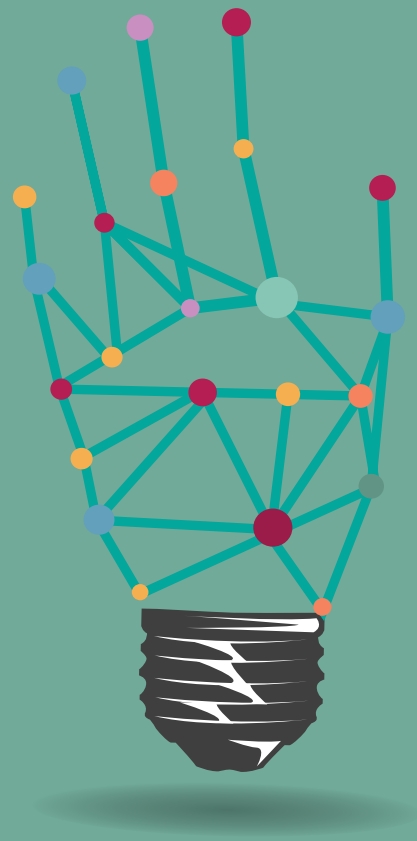

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Submitted

Intra- and inter-observer agreement on diagnosis and measurements of Dupuytren Disease severity

Chapter 4

Background

Dupuytren disease (DD) is a fibrosing disease affecting the palmar aponeurosis, and is mostly treated by surgery based on measurement of severity of the disease. Literature concerning the measurement reliability is scarce. This study aimed to determine the intra- and inter-observer agreement of four variables for diagnosing DD and its severity. One of them is a new measurement on the area of nodules and cords for measuring the severity in early stage of the disease.

Methods

An agreement study (n = 54) was performed by two trained investigators. Agreement was calculated based on an intraclass correlation coefficient (ICC) using a latent variable model on subjects for diagnosis and Tubiana stage. For total passive extension deficit (TPED) and the area of nodules and cords agreement was calculated with an ICC using a one-way random effects model with subject as random effect. Agreement for each variable was determined per finger.

Results

Inter-observer agreement was very good for diagnosing DD (ICC: 95.5–99.9) and good to very good for classifying Tubiana stage (ICC: 73.5–94.9). Agreements for area and TPED were moderate (middle finger) to very good (ICC: 48.4–98.6 and 45.0–99.5, respectively). Intra-observer agreement was slightly higher on average than inter-observer agreement.

Conclusions

Overall, the intra- and inter-observer agreement in diagnosing DD and determining its severity is high. Also, the newly introduced variable area of nodules and cords has high intra- and inter-observer agreement, indicating that it is a suitable method to measure disease severity.

Introduction

Dupuytren disease (DD) is a fibrosing disease affecting the palmar aponeurosis of the hand. This proliferation of fibrous tissue can lead to the formation of nodules and cords in the palm and fingers. These cords may contract, causing permanent flexion contractures of the fingers. Consequently, this often results in physical complaints.

The prevalence of DD ranges between 0.6 and 31.6% in the general population.[1] Despite conflicting results about the role of risk factors[2-5], older age and male sex are clearly associated with a higher prevalence.[6,7] In combination with the fact that the population is ageing and the life expectancy increases in Western countries[8,9], it can be expected that the number of patients suffering from DD will increase.

DD cannot be cured; treatment is aimed at reducing the flexion contractures of the fingers. These can be corrected using different treatment options[10], but most patients are treated surgically. Unfortunately, long-term recurrence rates are varying between 21–85%[11,12], depending on the type of treatment.[11] Because of these high recurrence rates, clinicians are often reluctant to perform surgery.

The decision to surgically intervene is usually based on the extension deficit (i.e. the severity of contracture) measured with a goniometer, and on the anamnestic progressiveness of this extension deficit in one or multiple fingers.[13] However, it is unclear how reliable these goniometry measurements are. Despite numerous reports concerning the reliability of goniometry in the upper extremity[14], there are only a few studies that have investigated the reliability of these measurements in finger joints.[15-17] In addition, these studies were performed in healthy subjects without hand disorders. Recently, one study was performed to determine the reliability of goniometry of the finger joints in DD patients.[18] However, only the active range of motion was determined in that study, instead of the passive extension deficit, which is often a decisive factor in the choice of treatment.[19]

The severity of DD is mainly determined using goniometry, and classified by the classification of Tubiana.[20] However, the majority of DD patients in the general population have mild disease without contractures.[6,7,21] Hence, it is not possible to measure disease progression in this patient group using goniometry. In two previous studies an alternative measurement method is reported, where the nodules and cords are encircled and registered using a photocopy of the hands.[22,23] However, it is unclear how the disease severity was quantified in these studies. To our knowledge, there is no alternative measurement to determine progression of disease in patients with mild disease. Therefore, we introduce the use of a tumorimeter to determine the size of nodules and cords. If this new measurement will be reliable, it can be used for example to study short term progression of disease, or to study occurrence and progression of recurrent disease.

The aim of this study is to determine the intra- and inter-observer agreement of four different measurement variables for diagnosing DD and its severity, namely: 1) the diagnosis itself, 2) Tubiana stage, 3) total passive extension deficit measured with a goniometer, and 4) the area of nodules and cords measured with a tumorimeter.

Methods

Participants

Adults with primary DD were asked to participate in this study. A sample size of 41-77 participants was needed to retrieve with 90% assurance an intra-class correlation (ICC) of 0.80 with a maximum confidence interval (CI) width of 0.3.[24] Therefore, taking non-response into account, 77 patients were asked to participate. Participants were included if they had primary DD in at least one hand, and were excluded if they were incapacitated. All participants gave written informed consent. The medical ethics committee of the University Medical Center Groningen approved this study.

Observers

The measurements were performed by two observers. The first is a medical doctor (RL) with extensive experience in diagnosing different stadia of DD. The second observer (DB) is a human movement scientist, and was trained in diagnosing DD prior to this study. During this training, she physically examined both hands of 50 DD patients with unilateral or bilateral disease and various disease stadia, without prior knowledge about the location of the nodules and cords. Thereafter, her findings were evaluated by the first observer, and both observers examined the hands together. Inconsistencies were then discussed to learn the second observer how to judge in these cases of doubt.

Outcome variables

Below, the different outcome variables are enumerated, whereby DD in the palm of the hand was registered as DD in the finger of the corresponding ray. For example, a palmar nodule in line with the ring finger was registered as DD in the ring finger. Nodules and cords of the first web space, for example originating

from the distal and proximal commissural ligaments, were recorded as an affected thumb.

1. Diagnosis of DD: This was determined by physical examination of the hands. The diagnosis of DD was registered binary (yes/no) for each finger separately.
2. Tubiana stage: The Tubiana stage was determined by transferring the TPED of each ray into this classification system.[25] To avoid ambiguity, the range of TPED of the original classification was adapted (Table 1).
3. Total passive extension deficit (TPED): This was measured in degrees using a Rolyan flexion-hyperextension finger goniometer (Smith&Nephew, Hull, UK, photo 1). To determine the passive extension deficit (PED), the participants placed their elbow on the table, and were asked to relax their hand and fingers. Then, the fingers were passively extended by the observer, until resistance was felt. At this point, the PED was measured of each joint separately. The joints were measured from proximal to distal, where the proximal joints were held in extension during the measurement of the distal joint. For the measurements at the fourth and fifth fingers, the observer blocked the carpometacarpal (CMC) joint in extension, to prevent measurement errors that can occur when the CMC joint is not blocked.[26] If applicable, hyperextension was also measured. The PED of the metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, and distal interphalangeal (DIP) joint were summed to acquire the TPED of each finger separately. The TPED was not measured in the thumb. TPED that was measured in a finger without DD (so due to other conditions), was not registered.
4. Area of the nodules and cords: For round-shaped nodules, a plastic tumorimeter (Pfizer Oncology, PharmaDesign Inc., China, photo 2) was used to determine the area in square centimeters. To determine the area of other shaped nodules or cords, the length and width (at three locations) was measured using the caliper on the tumorimeter. Afterwards, the area was calculated.

Table 1. Original and adapted version of the Tubiana classification system

Stage	Original classification	Our classification
0	No Dupuytren disease	No Dupuytren disease
N	Lesion without contracture	Lesion without contracture
1	0 to 45°	0 to 45°
2	45 to 90°	46 to 90°
3	90 to 135°	91 to 135°
4	> 135°	> 135°

Procedure

A schematic representation of the study procedure is given in Figure 1. The measurements took place at the outpatient clinic of the department of Plastic Surgery of the University Medical Center in Groningen, The Netherlands. First, the hands of the participants were examined only by the first observer. The nodules and cords were encircled using an erasable skin pencil. Then, the area of the nodules and cords was measured, followed by the PED of the affected fingers (when indicated).

To determine the intra-observer agreement, the participants returned 2-4 weeks later for the second measurements. This term was chosen in order to limit the possibility of disease progression, but to ensure that the observer was not able to remember the first measurements. The nodules and cords were encircled again, and the area and PED were measured by the first observer. In addition, a picture was made of both hands with the pencil lines. Thereafter, participants washed their hands thoroughly, to erase the pencil lines.

To determine the inter-observer agreement, the participants were examined

Photo 1. The finger goniometer.

Photo 2. The tumorimeter.

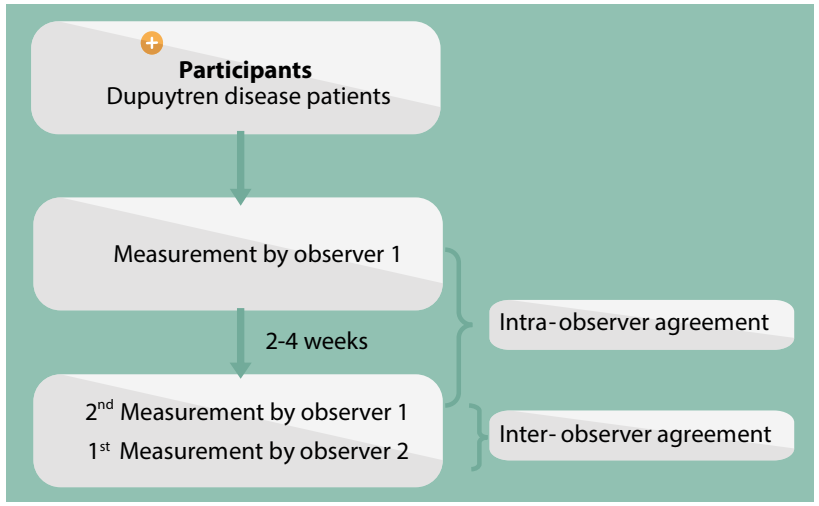

Figure 1. Schematic representation of the study procedure.

by the second observer immediately after the second measurement of the first observer, following the same procedure and using the same instruments. After performing all measurements, the findings of the two observers were compared to detect data entry errors. The pictures of the hands taken by the two observers were used to determine whether there was a data entry error or not.

Statistical analyses

Only measurements of primary affected hands were analyzed, and all analyses were performed for each ray separately. Descriptive statistics are presented by means with range for continuous data. Frequencies with percentages are given for nominal variables. Non-normal data (area of nodules and cords) were transformed with square root to achieve normality.

Agreement on DD and Tubiana was calculated with an intraclass correlation coefficient (ICC) using a latent variable for subjects underneath the binary or ordinal outcome. The continuous outcomes were analyzed with a one-way random effects model where subjects were considered the random effects on fingers with agreed positive diagnosis. Agreement was measured with and ICC and 95% confidence intervals were calculated with the Beta approximation.[27] Criteria for evaluation of ICC are shown in Table 2.[28]

Table 2. Criteria for evaluation of ICC

Value ICC	Strength of agreement
<20%	Poor
21-40%	Fair
41-60%	Moderate
61-80%	Good
81-100%	Very good

Results

In total, 54 participants (33 males and 21 females) with 78 primary affected hands were included in this study. Mean age of participants was 65.8 years (SD 9.2). DD was diagnosed by both observers in 194 fingers (Figure 2). In 8 fingers there was no consensus between the two observers about the presence of DD.

In Table 3, the differences in the area of nodules and cords and the TPED

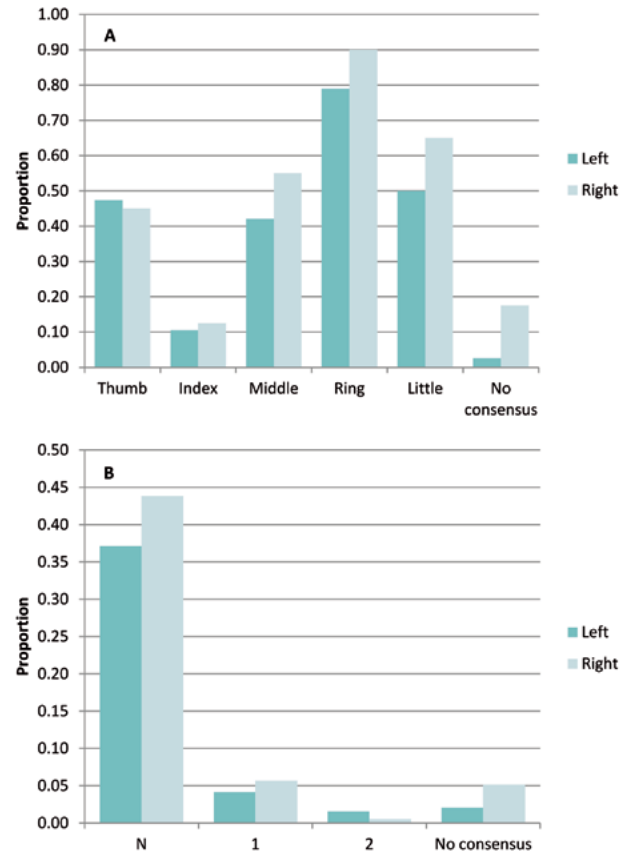

Figure 2. A) Occurrence of DD in different fingers, presented for each hand. B) Proportions of disease stages with respect to the total amount of affected fingers, presented for each hand.

between the first and the second measurement of observer 1 are presented. Also, the differences between the measurements of observer 1 and observer 2 are presented. For the intra-observer agreement, the positive mean differences indicate that the first measurement was larger than the second measurement, and vice versa. For the inter-observer agreement, the positive and negative mean differences indicate that the observers measured both larger as well as smaller values, compared to other observer. Regarding the measurements of the area and TPED, there were only small differences within the observer as well as between the observers. However, the dispersion is larger in the measurements of TPED compared to the area, especially with respect to the inter-observer comparison.

Table 3. Mean differences between observations in area of nodules and cords and in total passive extension deficit

Intra-observer comparison	**Left**		**Right**	
Δ Area	$cm^2 \pm SD$	Range	$cm^2 \pm SD$	Range
Thumb	0.00 ± 0.43	-0.48–1.15	-0.03 ± 0.35	-0.61–0.75
Index finger	-0.23 ± 0.30	-0.50–0.16	0.10 ± 0.32	-0.05–0.67
Middle finger	0.01 ± 0.30	-0.80–0.55	0.12 ± 0.54	-0.50–2.10
Ring finger	-0.07 ± 0.62	-1.94–1.46	-0.07 ± 0.52	-1.68–1.42
Little finger	-0.10 ± 0.41	-1.41–0.57	0.00 ± 0.67	-2.45–1.53
Δ TPED	° ± SD	Range	° ± SD	Range
Index finger	2.0 ± 1.0	0–4	0.4 ± 0.9	0–2
Middle finger	-0.1 ± 3.2	-8–9	0.5 ± 2.3	-4–8
Ring finger	0.9 ± 3.4	0–16	1.4 ± 4.6	-2–24
Little finger	-1.2 ± 3.9	-16–0	1.2 ± 5.4	-10–21

Inter-observer comparison	**Left**		**Right**	
Δ Area	$cm^2 \pm SD$	Range	$cm^2 \pm SD$	Range
Thumb	0.02 ± 0.46	-0.94–0.90	-0.27 ± 0.38	-0.82–0.40
Index finger	0.25 ± 0.44	-0.35–0.67	0.03 ± 0.17	-0.15–0.28
Middle finger	0.18 ± 0.47	-0.93–0.95	0.04 ± 0.59	-1.52–0.84
Ring finger	0.46 ± 0.91	-0.76–3.55	0.28 ± 0.46	-0.55–1.45
Little finger	0.22 ± 0.53	-0.50–2.01	0.45 ± 0.86	-1.15–3.22
Δ TPED	° ± SD	Range	° ± SD	Range
Index finger	1.0 ± 2.0	0–4	-2.0 ± 4.5	-10–0
Middle finger	1.8 ± 5.0	0–16	-0.6 ± 2.0	-8–2
Ring finger	-2.1 ± 10.3	-55–8	-2.3 ± 7.8	-36–0
Little finger	-0.4 ± 3.6	-10–10	-0.7 ± 4.7	-15–10

Agreement on DD and measurements

The agreement for diagnosing DD was very good. The smallest ICC for inter-observer agreement was observed for the little finger in the left hand: ICC [95%CI] = 95.5% [94.5% ; 96.4%]. All other fingers scored an ICC higher than 99.0%. The intra-observer agreement was only worse than the inter-observer agreement in the right ring finger (99.5% versus 99.9% respectively).

The ICCs for the other outcome measurements are reported in Tables 4a, b, and c. These Tables show that on average the intra-observer agreement is higher than the inter-observer agreement. The range in agreement is smallest for Tubiana stage (ICC 73.5–98.9), which is emphasized by the contingency table on Tubiana stage (Table 5). The range in agreement is largest for TPED (ICC 45.0–99.8). With respect to TPED, the agreements in the left middle finger are moderate. Regarding surface area, the agreement was very good in the majority of the fingers, however, agreement in the thumb and middle finger was considerably lower than in the other fingers. The measurement error of TPED ranges between 2.5° (right index finger) and 13.8° (left little finger) for the intra-observer agreement, and between 5.6° (left index finger) and 15.2° (left ring finger) for the inter-observer agreement.

Table 4a. Intraclass correlation coefficients for agreement on Tubiana stage with 95% confidence intervals

	Intra-observer agreement		**Inter-observer agreement**	
	Left	**Right**	**Left**	**Right**
Thumb	98.9 (98.9–99.0)	98.3 (98.2–98.5)	94.9 (93.8–95.8)	93.9 (92.4–95.3)
Index finger	93.9 (92.7–94.9)	94.2 (93.2–95.2)	86.7 (82.6–90.2)	86.6 (82.3–90.4)
Middle finger	85.9 (81.6–89.8)	83.4 (78.4–87.9)	91.8 (90.1–93.3)	88.9 (86.2–91.3)
Ring finger	93.1 (91.9–94.3)	98.2 (98.0–98.4)	73.5 (64.6–81.5)	88.4 (85.8–90.9)
Little finger	93.5 (92.0–94.9)	86.9 (83.1–90.4)	86.1 (82.8–89.0)	82.8 (77.3–87.6)

Table 4b. Intraclass correlation coefficients for the agreement of TPED measurements with 95% confidence intervals

	Intra-observer agreement		**Inter-observer agreement**	
	Left	**Right**	**Left**	**Right**
Thumb	NA[a]	NA[a]	NA[a]	NA[a]
Index finger	96.0 (84.6–99.9)	99.5 (98.4–100.0)	92.3 (71.1–99.9)	92.3 (74.3–99.7)
Middle finger	47.9 (15.8–81.1)	92.2 (84.9–97.2)	45.0 (12.9–79.9)	85.2 (72.5–94.5)
Ring finger	99.8 (99.6–99.9)	91.0 (84.6–95.8)	96.1 (92.9–98.3)	92.8 (87.7–96.6)
Little finger	97.4 (94.6–99.2)	94.8 (90.2–98.0)	98.5 (96.8–99.5)	96.8 (93.7–98.9)

a. Not applicable, because TPED was not measured in the thumb.

Table 4c. Intraclass correlation coefficients for the agreement of measurements of area of DD with 95% confidence intervals

	Intra-observer agreement		Inter-observer agreement	
	Left	Right	Left	Right
Thumb	82.2 (65.0–94.4)	50.8 (17.4–83.8)	72.9 (49.4–90.9)	63.3 (32.4–89.0)
Index finger	98.6 (94.5–100.0)	95.2 (83.8–99.8)	96.7 (87.0–100.0)	95.9 (85.8–99.9)
Middle finger	82.9 (65.6–94.9)	88.0 (77.1–95.6)	48.4 (16.3–81.3)	69.3 (47.1–87.5)
Ring finger	97.1 (94.8–98.8)	95.8 (92.7–98.1)	90.6 (83.4–95.9)	93.0 (88.0–96.7)
Little finger	93.8 (87.3–98.0)	91.9 (84.8–96.8)	87.6 (75.7–95.9)	93.6 (87.4–97.8)

Table 5. Contingency table on Tubiana stage

	Stage*	Observer 1			
		0	N	1	2
Observer 2	0	196	4	0	0
	N	2	157	4	0
	1	2	1	19	0
	2	0	0	1	4

* There were no patients with Tubiana stage >2 in our sample.

Discussion

The aim of this study was to determine the intra- and inter-observer agreement of different variables concerning diagnosis and disease severity in patients with primary DD. Secondly, we introduced a new variable to determine disease severity: area of nodules and cords, measured with a tumorimeter.

Regarding the diagnosis, the intra- and inter-observer agreement was very good in almost all fingers. The agreement was not 100%, which shows that despite the experience of the observer, there are always cases in which there is uncertainty about the presence of DD, for example because of the difficulty in distinguishing DD tissue from normal structures in cases with early DD. The high inter-observer agreement on diagnosis indicates that a relatively inexperienced observer is able to recognize DD after a short training period, even in participants with an early stage of DD without contractures. This is an important finding, since in several studies the results are sometimes questioned if the study was performed by a less experienced investigator.[3,5,7] In addition, the agreement on Tubiana stage was also very good.

One of the aims of this study was to investigate the agreement on measurement of TPED. Since the PED of thumb's MP and IP are very much influenced by the position of the CMC, the thumb was excluded from this study. With respect to TPED

in the remaining fingers, the intra- and inter-observer agreement was very good, indicating that reliable values can be obtained when consecutive measurements are performed by the same or another physician in clinical practice. However, both the intra- and inter-observer agreement in the left middle finger were moderate. It could be that TPED is harder to measure on the left hand when the investigator is right handed. Another possibility is that dynamism during the measurements of TPED is responsible for this lack of agreement. Dynamism is the phenomena that the extension deficit of one joint can be influenced by the position of the other joint, especially when a contracture affects both the MCP and PIP joint.[29] However, if dynamism is responsible for the low agreement, it would be expected that the agreement in some other fingers was low too. Furthermore, since both observers measured participants in the same way, the effect of dynamism on the agreement will be negligible. The low agreement might also be caused by difficulties with the measurements in patients with additional conditions, such as arthritis or knuckle pads. Such conditions often result in thickened PIP or DIP joints, which complicates the measurements, and can lead to an overestimation of the extension deficit.

In the literature, many different methods to measure extension deficit (ED) are reported: active extension loss[30], total ED[31], and total passive ED[32]. In some articles, the used method to measure ED is not reported at all[33-35], while the method is likely to influence the results. These different measurement methods complicate the comparison of different studies. It is favorable to use one and the same method, and our results show that TPED might be a good choice. However, the large ranges of the TPED in some fingers underline the necessity of taking measurement errors into account, especially in case the TPED is used to decide for a surgical treatment. In the current clinical practice, it is advised to round the range of motion measurements to the nearest ten for each joint.[36] This suggests that measurements of TPED can have a dispersion of 15°, because TPED consists of measurements of three joints. Our results show that on average the expected maximum error of unrounded measurements is at most 15°, indicating that it is unnecessary to round TPED measurements. It should be noted that the actual difference between observers in individual patients can be larger. With this in mind, we recommend that in clinical practice the decision to perform surgery should not only be based on TPED, but also on change over time in combination with the complaints that the patient report. Future studies should be performed to provide more insight in the reliability of the different methods to measure ED, and to study the natural disease

progress.

With respect to the measurements of the area of nodules and cords, the intra- and inter-observer agreement were good to very good in all fingers, except for the left middle finger and the right thumb. The latter might be explained by the fact that the distal and proximal transversal commissural ligaments in the first web space can easily be mistaken for DD cords in participants with thin skin.[37,38] Furthermore, the anatomy of the first web space is complex, which complicates the distinction between healthy and mildly diseased tissue. Our results indicate that this newly introduced measurement is accurate to determine the disease severity in patients without contractures. This adds value to clinical and scientific practice, since this measurement can be used to study disease progression in patients with mild DD, and to study (early) recurrence after treatment.

This is the first study that investigates both intra- and inter-observer agreement in patients with DD. A strength of this study is the large number of 194 primary affected fingers. To compare, the only other study on reliability of goniometry measurements in patients with DD included 13 rays and found ICCs that ranged from 83.2–97.3%.[18] In addition, we performed a sample size determination beforehand, and were able to include a sufficient number of participants. This enlarges the reliability of our results.

A limitation of this study is that the measurements were performed with non-validated instruments (tumorimeter, goniometer). However, it is unlikely that this led to bias, because the observers used exactly the same instruments interchangeably. Thereby, the use of these instruments enlarges the external validity, as it mimics the daily clinical practice. A second limitation is that the period between the first and the second visit varied between the participants. This could have negatively influenced the intra-observer agreement, since it is possible that the disease progressed between the observations. However, based on the literature concerning DD progression[30,39], it is questionable whether considerable disease progression could occur in this time frame of 2-4 weeks. If some change has occurred, the ICCs are underestimated.

In conclusion, diagnosing DD and determining its severity using Tubiana classification, TPED, and the area of nodules and cords provides reliable findings with respect to both the intra- and inter-observer agreement. The agreement is high in general, but measurements are more difficult for the thumb and middle finger. The newly introduced measurement of surface area of nodules and cords is a reliable method to study disease severity in patients with mild DD without contractures.

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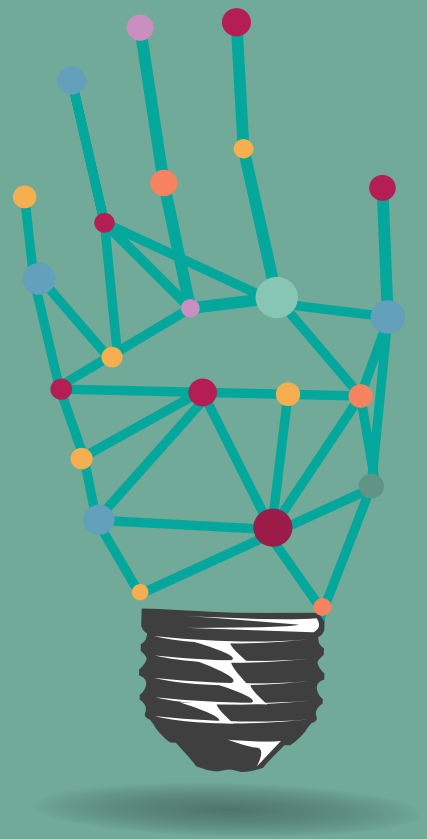

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Patterns of Dupuytren Disease in fingers; studying correlations with a multivariate ordinal logit model

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Chapter 5

Objective

Dupuytren disease (DD) affects fingers in a variable fashion. Knowledge about specific disease patterns (phenotype) based on location and severity of the disease is lacking.

Methods

In this cross-sectional study, 344 primary affected hands with DD were physically examined. Pearson's correlation coefficient between the coexistence of DD in pairs of fingers was calculated, and agglomerative hierarchical clustering was applied to identify possible clusters of affected fingers. With a multivariate ordinal logit model we studied the correlation on severity, taking into account age and gender, and tested hypotheses on independence between groups of fingers.

Results

The ring finger was most frequently affected by DD, and contractures were seen in 15.1% of affected rays. The severity of thumb and index finger, middle and ring finger, and the middle and little finger was significantly correlated. Occurrences in pairs of fingers were highest in the middle and ring finger, and lowest in the thumb and index finger. Correlation between the ring and little finger, and a correlation between fingers from the ulnar and radial side could not be demonstrated.

Conclusions

Rays on the ulnar side of the hand are predominantly affected. The middle finger is substantially correlated with other fingers on the ulnar side, the thumb and index finger are correlated, however there was no evidence that the ulnar side and the radial side were correlated in any way, which suggests that occurrence on one side of the hand does not predict DD on the other side of the hand.

Introduction

Dupuytren disease (DD) is an incurable fibromatosis of the hand and fingers, giving rise to the development of skin pitting and subcutaneous nodules in the palm. At a later stage of disease cords appear that connect the nodules and may contract the fingers into a flexed position. A contracture can occur isolated in a single joint, but may also involve more joints of a single ray or even multiple rays, whereby the metacarpophalangeal joints (MCPJ), proximal interphalangeal joints (PIPJ), and distal interphalangeal joints (DIPJ) are affected in decreasing order. The disease is usually located on the ulnar side of the hand, and in particular the ring finger and the little finger are frequently affected.[1-3]

Several authors have described the patterns of occurrence of DD in multiple fingers empirically. Meyerding noticed that the combination of an affected ring and little finger occurred most often, followed by the combination of an affected third, fourth, and fifth digit.[4] In addition, Tubiana has stated that isolated radial side involvement in DD is rare, and that radial involvement in most cases is associated with an affected ulnar side.[5] Milner et al. found that patients with a severely affected thumb which had required surgery, were on average eight years older, and had suffered significantly longer from DD than patients with a mildly affected radial side. Furthermore, these patients with severe disease of the thumb suffered from ulnar disease which repeatedly had required surgery, suggesting an intractable form of disease.[3,6] Orlando reported that in most hands two rays are affected by DD, followed by one finger and three fingers. Affection of four or even five fingers was rarely seen.[7] A previous study of ours showed an average of 2.7 affected rays per patient.[2]

In summary, the frequency in which each ray is affected has been described previously, as well as intra operative findings in relatively small samples[8], but firm statistical substantiation is lacking. The consequence is that certain findings may be spurious and not tested appropriately. For instance, the higher frequency of an affected ring and little finger may well be determined by the higher occurrences in these fingers, and may not be more frequent than expected by chance. This may be true also for other pairs, and additionally for triplets, quadruples, or even for the affection of all rays of one hand.

Furthermore, the existence of specific disease patterns (phenotype) based on location and severity of the disease has never been studied before. Therefore, the aim of this study is firstly to investigate the patterns of occurrence and severity of primary DD in both men and women, and secondly to test the earlier suggested correlations in DD occurrence between the little and ring finger, but more importantly between the ulnar and radial side of the hand.

Methods

Participants and physical examination

To obtain a representative cross-sectional set of patients with DD, we included 105 patients from the general population of the northern Netherlands[2], as well as 134 patients from the outpatient clinic of the Department of Plastic Surgery of the University Medical Center Groningen. This study was approved by the institutional ethics review board.

Both hands of all included patients were physically examined by the first author at the outpatient clinic. Signs of DD, including presence of subcutaneous nodules and fascial cords, with or without finger contractures, were noted for each ray of each hand. The severity of flexion contractures was measured with a goniometer, and the passive extension deficit was noted in degrees for each joint separately. Thereafter, the severity of disease was categorized using the classification of Tubiana[9], in which stage N refers to affection with only a nodus or cord without contracture[10] (Table 1).

Statistical analyses

Descriptive statistics of our population were calculated first. Furthermore, Pearson's correlation coefficient between the coexistence of DD among pairs of fingers in each hand separately was calculated and tested for its statistical significance. We performed a post-hoc power analysis, to calculate what minimal correlation we could detect with our sample size.[11]

To identify possible occurrence of patterns in fingers with DD, a hierarchical cluster analysis was conducted, assuming that patterns would be similar in both hands. The measure of similarity between fingers was based on Jaccard[12], and the complete-linkage method[13] was applied to form clusters of fingers. Agglomerative hierarchical clustering (from bottom to top) was used.[14]

To investigate the influence of gender and age on the coexistence of DD, and to evaluate the patterns of severity, a multivariate ordinal logit model was fitted to the Tubiana stage of all five fingers simultaneously (assuming that patterns are similar in both hands again). For this statistical analysis we collapsed the three

most severe categories of Tubiana into one category. This multivariate model is similar to a probit model[15], but it was altered to be able to fit logits instead of probits, so that the effects of age and gender have interpretations similar to logistic regression. Instead of correlations on the occurrence, this multivariate model provides correlations on the severity between fingers, corrected for covariates. To obtain confidence intervals on the parameter estimates of the multivariate model, bootstrapping of 1000 samples was applied. Based on the multivariate model, the predicted probabilities of occurrence of DD in multiple fingers simultaneously are presented, and compared to the probabilities based on independence. If fingers are affected completely independent from each other, it can be expected that they co-occur with a frequency that equals the product of the occurrence rates of the individually affected fingers. Independency on severity between the radial side and ulnar side was tested with the likelihood ratio test.

The statistical terminology is explained in more detail in the appendix.

Table 1. Tubiana classification

Stage	Total passive extension deficit
0	No lesion
N	0°
1	1-45°
2	46-90°
3	91-135°
4	>135°

Results

In this study, data of 152 (63.6%) males and 87 (36.4%) females were used. Mean age of patients was 65.4 years (SD 9.8), and 344 hands were affected. The ulnar side of the hand was predominantly affected; the most frequently affected ray was the ring finger, followed by the little finger and middle finger (Figure 1).

Pearson's correlation coefficient for the coexistence of DD between fingers of both hands separately is provided in Table 2. We found that the thumb and index finger are significantly positively correlated in both hands (left 0.149; right 0.205), as well as the middle finger and the little finger of the left hand (0.262). Besides this, no high correlations were observed. Note that a correlation of 0.15 or higher could be detected with at least 80% power with the sample size of our cohort.[11]

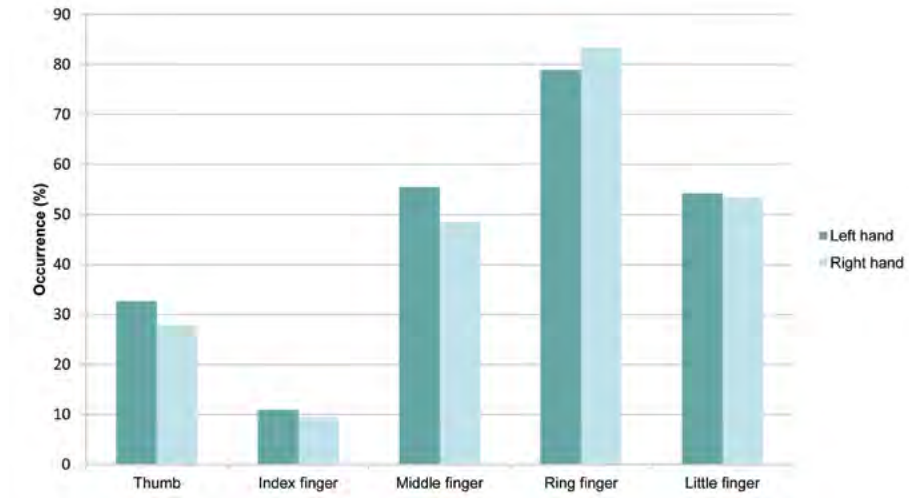

Figure 1. Occurrence of rays affected with DD per hand.

Assuming that the patterns would be the same across hands (which seems plausible considering the results from Figure 1 and Table 2), the dendrogram of the hierarchical clustering demonstrates that the middle finger and the ring finger should form the first cluster (Figure 2). This cluster was thereafter sequentially enlarged with the little finger, the thumb and the index finger. However, the short length(s) of the arms in the dendrogram suggest that the middle, ring, and little finger together form one cluster, while based on the longer length(s) of the arms, the thumb and the index finger should be seen as separate clusters. Thus three clusters were formed by the hierarchical clustering, where the ulnar side seems separate from the radial side.

Table 2. Pearson's correlation coefficient for the coexistence of DD among fingers on the left hand (lower triangle) and right hand (upper triangle)

	Thumb	Index finger	Middle finger	Ring finger	Little finger
Thumb	NA	**0.205****	0.084	0.028	0.079
Index finger	**0.149***	NA	0.090	-0.019	0.141
Middle finger	0.133	0.054	NA	0.019	0.127
Ring finger	0.002	-0.134	0.099	NA	-0.035
Little finger	0.026	0.025	**0.262****	0.002	NA

* Significant at 0.05. ** Significant at 0.01. NA: not applicable.

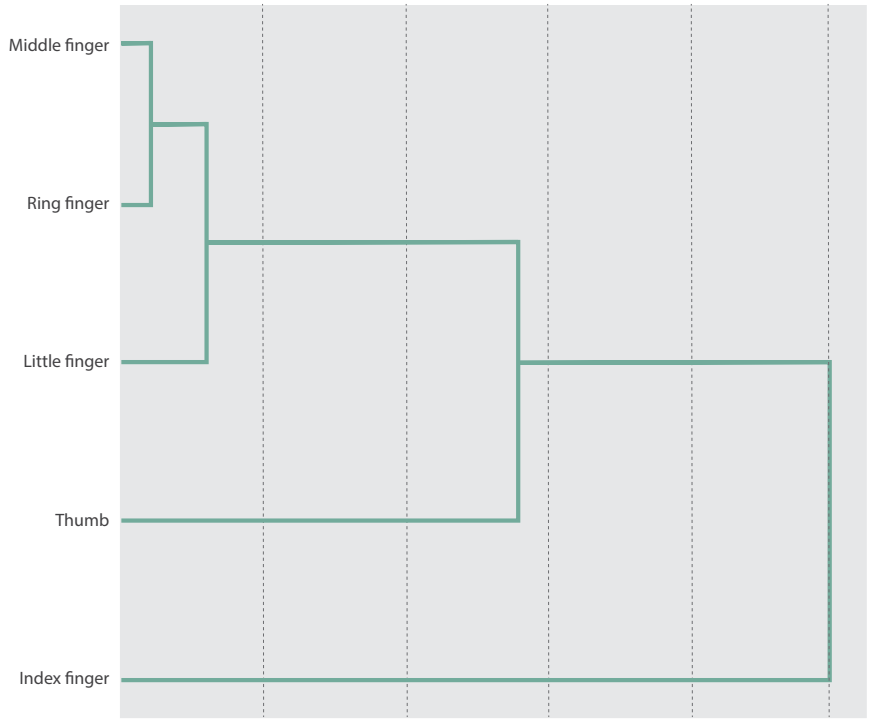

Figure 2. Dendrogram of the hierarchical clustering of the occurrence of fingers using Jaccard distance and complete linkage.

Table 3 shows the distribution of the severity of DD based on Tubiana stage. In most affected rays only nodules and cords were found, without an extension deficit. Contractures were seen in 15.1% of the affected rays.

None of the identified patterns so far used information on the Tubiana stage, and the results were not adjusted for covariates such as gender and age. Therefore, a multivariate logit model on severity—which takes age and gender into account—was fitted to the data. No effect of age and gender on the severity of DD could be demonstrated (gender OR: 1.27 [0.98 ; 1.64]; age OR: 1.06 [0.95 ; 1.24]). The correlation coefficients with 95% confidence intervals for severity of DD between pairs of fingers are presented in Table 4. There was a significant correlation between thumb and index finger, the middle and ring finger, and the middle and little finger. The significant positive correlations imply that those pairs occur more frequently than can be expected based on independence, and that a more severe disease of, for example, the middle finger is accompanied by more severe disease of the ring finger. The radial side (thumb and index) and the ring finger, as well as the ring finger and little finger, seem to be negatively correlated, although not significant.

The multivariate logit model makes it also possible to predict the occurrences of DD in single, pairs, triplets, quadruples, and quintets of rays for both genders at different ages. Since age only had a minor effect on the severity of DD in fingers, we report only the results at age 65 years (the average age of the sample). In Table 5, the highest predicted occurrence of DD in pairs of fingers was observed in the middle and ring finger at 46.2% [39.7 ; 53.0] for males and 39.7% [32.8 ; 46.7] for females. DD in any pair of fingers seem to occur least frequent in the thumb and index finger at 5.4% [3.0 ; 8.3] for males and 3.7% [1.9 ; 6.3] for females. The highest predicted occurrence of all triplet combinations is a combination of the middle, ring and little finger with a occurrence of 29.5% [23.4 ; 35.4] for males and 23.2% [17.3 ; 29.5] for females. For quintets the occurrence decreases to 2.1% [1.0 ; 3.5] for males and 1.2% [0.4 ; 2.3] for females. As expected from the occurrences of individual fingers and pairs, the triplet and quadruple combinations which include fingers from the ulnar side are more prevalent.

Table 3. Frequency (percentage) of severity of DD per finger

	Tubiana stage			
	Unaffected	N	1	≥ 2
Thumb	240 (69.8)	103 (29.9)	1 (0.3)	-
Index finger	309 (89.8)	26 (7.6)	8 (2.3)	1 (0.3)
Middle finger	165 (48.0)	159 (46.2)	16 (4.6)	4 (1.2)
Ring finger	65 (18.9)	233 (67.7)	44 (12.8)	2 (0.6)
Little finger	159 (46.2)	143 (41.6)	32 (9.3)	10 (2.9)

Table 4. Correlation coefficients with 95% confidence intervals for severity of DD between pairs of fingers based on the multivariate logit model

	Index finger	Middle finger	Ring finger	Little finger
Thumb	**0.22*** [0.01 ; 0.42]	0.16 [-0.04 ; 0.34]	-0.009 [-0.24 ; 0.21]	0.09 [-0.08 ; 0.25]
Index finger	NA	0.12 [-0.12 ; 0.35]	-0.17 [-0.39 ; 0.06]	0.14 [-0.06 ; 0.35]
Middle finger		NA	**0.29**** [0.10 ; 0.47]	**0.17*** [0.02 ; 0.31]
Ring finger			NA	-0.12 [-0.30 ; 0.05]

Significant correlations are shown in bold.
* Significant at 0.05.
** Significant at 0.01.

The correlations in occurrence (Table 2) and severity (Table 4) in DD between the little finger and ring finger were not strong. We tested the hypothesis of independence by comparing the predicted occurrence of DD in these fingers with the product of the predicted occurrences of the single fingers. The p-value was determined at P = 0.491 for males and P = 0.376 for females, which suggests that we cannot demonstrate a correlation between the little and ring finger. We also tested, in a similar fashion, whether the ulnar and radial side are independent. The predicted occurrence of the quintet is quite close to the product of the predicted occurrence of the triplet "little, ring, and middle finger" and the pair "thumb and index finger" (males: P = 0.202; females: P = 0.218). However, since the predicted occurrences are quite small, we also tested this hypothesis with the likelihood ratio test, by comparing our multivariate logit model with a similar multivariate logit model where all of the correlations on severity between fingers on the radial side and fingers on the ulnar side were set equal to zero. Again, independence between the ulnar side and radial side could not be rejected (LRT = 9.53; df = 6; P = 0.146).

Table 5. Predicted occurrences (%) of DD with 95% confidence intervals in single and combinations of fingers for males and females separately at age 65 years

One or two fingers	Occurrence		Three or more fingers	Occurrence	
	Males	Females		Males	Females
Thumb (1)	30.9 [25.6 ; 36.4]	26.1 [20.8 ; 31.6]	**123**	3.7 [1.9 ; 5.8]	2.4 [1.1 ; 4.0]
Index (2)	12.8 [8.8 ; 17.4]	10.4 [6.8 ; 14.9]	**124**	3.9 [2.0 ; 6.2]	2.4 [1.0 ; 4.5]
Middle (3)	53.8 [47.8 ; 60.1]	48.7 [41.3 ; 54.3]	**125**	3.9 [2.1 ; 6.2]	2.5 [1.2 ; 4.5]
Ring (4)	77.3 [73.0 ; 81.1]	72.9 [67.5 ; 77.8]	**134**	16.3 [11.9 ; 21.0]	12.1 [7.9 ; 16.7]
Little (5)	59.5 [53.0 ; 65.1]	53.6 [46.7 ; 59.9]	**135**	13.3 [9.4 ; 17.7]	9.5 [6.1 ; 14.0]
12	5.4 [3.0 ; 8.3]	3.7 [1.9 ; 6.3]	**145**	15.5 [11.5 ; 20.0]	11.2 [7.2 ; 16.1]
13	19.4 [14.8 ; 24.1]	14.9 [10.5 ; 19.9]	**234**	5.7 [3.1 ; 8.9]	3.8 [1.8 ; 6.4]
14	24.5 [19.4 ; 29.6]	19.4 [14.0 ; 25.1]	**235**	5.4 [2.9 ; 8.5]	3.6 [1.7 ; 6.2]
15	20.2 [15.6 ; 25.1]	15.6 [11.2 ; 20.8]	**245**	5.6 [3.2 ; 8.5]	3.7 [1.7 ; 6.5]
23	7.4 [4.3 ; 11.0]	5.3 [2.8 ; 8.3]	**345**	29.5 [23.4 ; 35.4]	23.2 [17.3 ; 29.5]
24	8.3 [5.1 ; 12.0]	5.8 [3.1 ; 9.4]	**1234**	2.8 [1.4 ; 4.7]	1.7 [0.7 ; 3.1]
25	8.2 [5.0 ; 12.0]	5.9 [3.1 ; 9.3]	**1235**	2.8 [1.3 ; 4.6]	1.7 [0.7 ; 3.1]
34	46.2 [39.7 ; 53.0]	39.7 [32.8 ; 46.7]	**1245**	2.7 [1.4 ; 4.5]	1.6 [0.6 ; 3.2]
35	35.5 [29.4 ; 41.5]	29.2 [23.1 ; 35.5]	**1345**	11.0 [7.6 ; 15.2]	7.5 [4.5 ; 11.7]
45	45.9 [39.5 ; 51.8]	38.7 [31.5 ; 45.8]	**2345**	4.1 [2.1 ; 6.7]	2.6 [1.0 ; 4.6]
-	-	-	**12345**	2.1 [1.0 ; 3.5]	1.2 [0.4 ; 2.3]

Discussion

The aim of this study was to scrutinize the phenotype, i.e. disease patterns, of primary DD in men and women. When studying the phenotype of DD, it is important to realize that supposed patterns are dependent on the number of times the individual rays are affected. For example, the ring finger and little finger are most frequently affected. As a consequence, these fingers will often be seen affected with DD in combination with other affected rays, and one could therefore inadvertently conclude that there is a disease pattern. However, true patterns only exist when they appear more often than is expected based on the individual frequencies. In our study, we have investigated this, in particular on patterns that were recognized in the past.

Several aspects should be noted regarding the etiology of the phenotype. The anatomy of the hand is very complex, and has been the subject of numerous publications. In addition, several authors have tried to elucidate which anatomical structures are affected in DD. Tubiana has written about DD on the radial side of the hand, where a close relation exists between the thumb and index finger through the distal and proximal transverse commissural ligaments.[5] Based on this anatomical finding it is conceivable that thumb and index finger affection is correlated. This correlation could be proven both in the occurrence, and with respect to the severity of DD. Tubiana also suggested that isolated DD of the radial side is rare, however, we could not demonstrate that the radial and ulnar side were correlated. Thus, we conclude that the in past literature frequently observed occurrence of an affected radial side in combination with a single ray or multiple rays from the ulnar side, is just explained by the high occurrences of DD in fingers in the ulnar side, and low frequency in the radial side. Indeed, our results show that the ring finger ray is frequently affected, while the disease in the radial rays of the hand, especially the index finger, is relatively rare. Furthermore, in our sample with only primary affected hands, the minority of rays had a passive extension deficit. These findings on occurrence are in agreement with the results of previous research.[3,16,17] In our analyses we assumed that severity of disease does not affect the correlations between fingers. This assumption implies that late stage disease would show similar disease patterns as early stage disease, but with higher levels of severity. This is difficult to test, but the goodness-of-fit test of our statistical model did not show a lack-of-fit, which we interpreted as evidence for our assumptions. Therefore, we expect that a higher prevalence of contractures in our sample would

not have changed the conclusions.

McGrouther has described different layers of longitudinal fibers in the distal palm, from which the most superficial fibers insert into the dermis of the distal palm and proximal phalanx. These fibers are especially prominent in the middle and ring finger[18], and this might be an explanation for the correlation between these two fingers. Besides, these fibers are also seen in the little finger, and this supports the correlation between the middle and little finger, and the high predicted occurrences of the triplet combination of the middle, ring and little finger.

Besides anatomical variations, at present unknown molecular abnormalities of the extracellular matrix (ECM) as well as cytokines and growth factors that are associated with pathogenesis of DD, may play a role in the phenotype. Although results of different studies are not unambiguous, it has been suggested that ECM-proteins, such as collagen, periostin and β-catenin stimulate the proliferation, differentiation, and invasiveness of fibroblasts.[19,20] Furthermore, oxidative stress is thought to be involved in the pathogenesis of DD.[20] Hypoxia activates the xanthine oxidase pathway, eventually resulting in formation of oxygen free radicals, which are thought to stimulate myofibroblast proliferation.[19,21] Based on these pathogenic processes, it is possible that areas in the hand that contain more ECM-proteins or are exposed to hypoxia, will be more affected with DD. In this respect, environmental risk factors that are thought to be associated with DD, such as heavy manual work and exposure to vibration[22], may also affect the phenotype. It is conceivable that DD will be more present in areas in the hand where the largest forces are applied to. Since the little and ring finger are the fingers that are predominantly used to grip and hold objects, this might explain their more frequent affection, although we could not demonstrate a correlation between this pair of fingers. However, more fundamental research is needed to elucidate the effect of these external forces on various tissues. Furthermore, attention should be paid to the effect of the amount of force, the duration of exposure, and the recovery time between exposure.

Dolmans et al. identified genetic risk factors that contribute to DD. The presence of nine specific SNPs can be used to calculate a genetic risk score for each patient.[23,24] Patients with certain clinical findings, such as a positive family history or ectopic lesions, had a higher genetic risk score.[24] It would be interesting to study whether this genetic risk score is associated with certain disease patterns. For instance, whether patients that carry more risk alleles have a more extensive phenotype.

One of the strengths of this cross-sectional study is the large number of primary affected hands that were included. Furthermore, the severity of disease in all cases was measured by only one observer and categorized using the well known classification of Tubiana.[9] However, our sample represents patients from the northern Netherlands alone, and the findings of our study may not necessarily be transferable to other parts of the world. Indeed, it has been suggested that race and geographical location might play a role in the onset of the disease, and will therefore influence the prevalence of DD. On the other hand, there is no clear influence of race and geographical location on prevalence[25], which makes it even more difficult to understand the potential influence of geography on disease patterns and correlations. Previous publications from Europe[3,5] and Japan[6], showed a comparable distribution of occurrence of DD among fingers. Thus, we expect that our results will also be applicable to patients with DD from other countries, but this needs to be confirmed with other studies.

Previous studies on the phenotype of DD were most often observational studies without firm statistical analyses.[3-5] Therefore, our study with agglomerative hierarchical clustering and a multivariate ordinal logit model adds great value to the existing literature.

In articles studying disease patterns or clusters of disease, hierarchical clustering is a frequently used method.[26-28] However, it is an explorative analysis, and there are several disadvantages to this method. Firstly, errors in clustering methods for binary data may be quite substantial, although an evaluation revealed that our method, using Jaccard's distance and complete linkage, is one of the best methods to choose.[13] Secondly, this analysis will forcedly create clusters, even when in the data no natural clusters exist.[29] A third drawback is the inability to address risk factors with this explorative analysis.

In our multivariate model these disadvantages do not apply, and we included age and gender as covariates. Therefore, our results are applicable to a broad population. Although there was no statistically significant relation between severity of DD and gender and age, the results suggest that males and older patients have more severe disease. It has been stated that younger patients have a more aggressive form of the disease with a higher recurrence rate[30], so consequently these patients will have a more severe disease already at younger ages, reducing the overall effect of age on severity. It might have been interesting to include age of onset or duration of disease as well. However, we noticed that patients have

difficulty remembering the exact age of onset of the disease, which makes it unreliable to use this information.

In conclusion, our study substantiates that the ulnar side of the hand is predominantly affected in DD. In addition, regarding severity of DD, we found a significant correlation between thumb and index finger, middle and ring finger, and the middle and little finger. The ulnar and radial side of the hand do not seem to be significantly correlated in any way, nor could we demonstrate a correlation between the little and ring finger. Knowledge of these phenotypes is a first step towards further analysis of the role of the genotype in causing the various forms of DD.

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Appendix

Cluster analysis: Cluster analysis is a statistical technique to discover homogeneous subgroups based on a set of measurements. In practice, a cluster analysis is the end product of a series of analytical decisions. This series of analytic decisions typically involve choices about what objects to cluster, what *proximity measure* to use to determine similarity or dissimilarity among the objects, and what *type of clustering algorithm* to use.[1] In our data, we aimed to cluster fingers that were affected with DD. The measures of proximity and type of clustering algorithms are explained below.

Measures of proximity: To identify clusters of observations (i.e. combinations of affected fingers) in the data, it is important to know how similar individual observations (i.e. individual affected fingers) are, or how far apart they are. For binary data (a finger is affected with DD or not) several measures of similarity can be used, all based on measures of a 2x2 contingency table. We used *Jaccard's coefficient*. This method only gives weight to the similarity of two fingers when DD is present in these fingers. Fingers without DD are ignored in this similarity measure.

Besides the proximity between two individual observations (for example affected thumb and affected little finger), it is important to measure the dissimilarity of groups of observations in a cluster analysis. This inter-group proximity is based on the inter-individual proximity. In the complete linkage cluster method, which we used, the inter-group dissimilarity is defined as the largest distance between two individual observations, one from each group.[2] This is also known as furthest-neighbor distance.[3]

Type of clustering algorithm: Clustering algorithms can be classified as hierarchical or non-hierarchical. Hierarchical algorithms are most appropriate for classification when objects are related via some underlying systematic structure.[1] Hierarchical algorithms are further classified according to whether the algorithm proceeds by successively merging individual observations into groups (*agglomerative method*) or starts with one large cluster and separates the observations into smaller groups (divisive method). Agglomerative methods are most widely used.[1,3]

In **agglomerative hierarchical clustering** the clusters are formed in several steps. It starts with all single objects as separate clusters, in our case all five fingers are seen as separate cluster at the beginning of the analysis. Successively these objects are grouped into larger clusters until the final grouping contains all the

original objects in one group. A dendogram illustrates which fusions are made in each step of the analysis.[4] For example, our dendogram (Figure 2 in this chapter) shows that in the first step the middle finger and ring finger are clustered (and thus are most similar compared to other combinations). In the following step the little finger was added to this first cluster, keeping the thumb and index finger still as single clusters.

With a **multivariate ordinal logit model** an ordinal logistic regression-like analysis was performed. This model is suitable for categorical data with ordered categories (i.e. Tubiana stage), measured at multiple time points or locations (i.e. five fingers).[5] The model takes into account that observations on one hand could be correlated. In addition, covariates can be included in the statistical model to distinguish in severity level between subgroups of patients. In our paper, we used this model to calculate the correlations on the severity between fingers, corrected for age and gender.

Bootstrapping: method to obtain confidence intervals on the parameter estimates of the multivariate model.

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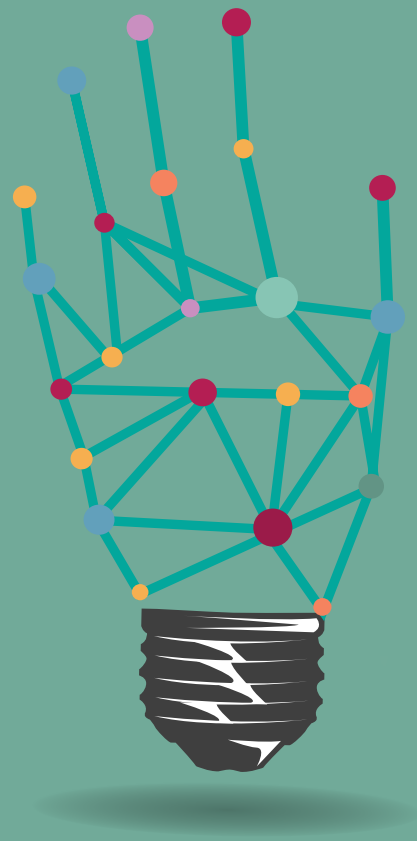

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Clusters in short term disease course in participants with primary Dupuytren Disease

Chapter 6

Objective

The course of Dupuytren disease (DD) is thought to be progressive, however, the speed and pattern of development of the disease differs between patients, and knowledge about the short term disease course is incomplete.

Methods

The course of DD was prospectively objectified at intervals of 3-6 months in 247 participants with primary DD by measuring surface area of nodules and cords, and total passive extension deficit (TPED). The association between surface area and Tubiana stage was tested with generalized estimating equations (GEE). Changes over time in surface area and TPED were studied with a linear mixed model for each ray separately. Latent class models were used to cluster change profiles.

Results

A high association was found between surface area and Tubiana stage (OR 3.24; 95% CI 2.55-4.13). On average, in one year the surface area increased with 0.22 cm^2 and TPED with 5.5 degrees; however, the variance between participants was large. Regarding change in surface area and TPED different clusters were observed; progression of disease was seen, but also stability and even regression. Study cases with a smaller surface area at baseline were more likely to exhibit regression. No other typical factors could be linked to disease course.

Conclusions

This study shows that DD is not always progressive, and that up to 75% of cases has a different short-term disease course. This should be taken into account when evaluating the effects of treatment for early-phase DD, and in the design of future studies.

Introduction

Dupuytren disease (DD) is a chronic fibromatosis of the palmar fascia of the hand and fingers. The etiology and pathogenesis have not been fully elucidated; however, the disease has a genetic origin.[1] Besides, several factors such as smoking, excessive alcohol consumption, male gender, diabetes mellitus, epilepsy and performing heavy manual labour are thought to increase the probability of emergence of the disease[2-6], although the results of different studies are not consistent. Prevalence of DD in the general population of Western countries can be estimated between 0.3 and 31.6%.[7] The disease is mainly diagnosed in elderly white males of Northern European descent, and prevalence rises with increasing age.[8-11]

Clinically, DD starts with subcutaneous nodules in the palm of the hand, and when in a later stage cords appear that shorten, skin pits may occur and the fingers can be pulled into a flexed position. A flexion contracture can affect a single joint, but also multiple adjacent joints of a finger, whereby the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints are most frequently involved.

Some people will only develop small lumps which do not progress into cords and contractures, while others will develop a severe contracture of the finger(s), so progression is unpredictable. A limited number of authors have studied the clinical disease course of DD. Millesi diagnosed DD in about 40% of patients who were previously unaffected, after a follow up of 5 years.[12] Reilly found, after an average follow up of 8.7 years, that in 51% of patients with nodules the disease had progressed into cords.[13] In the study of Gudmundsson, 34.6% of the patients with DD had developed contractures or had been operated after 18 years. Of the control group without DD, 52.5% had developed clinical signs of DD in this period.[14] These long term studies suggest that the disease is progressive over time. However, there were only two moments of assessment, and as a result possible short-term fluctuations in disease course have not been defined.

Histological studies show that the course of development of DD can include periods of exacerbation and regression.[12,15] Three stages have been described in DD: a proliferative stage, an involutional stage, and a residual stage. During these stages, the cells in nodules are subjected to maturation, collagen becomes aligned and contraction occurs.[15] When the disease progresses during these stages, the amount of immature collagen type III decreases and at the same moment the amount of mature collagen type I increases.[16] Furthermore, the stages in the development of DD can be repeated frequently, leading to periods of activity and inactivity.[12] It is unknown how this histological process manifests clinically in patients with DD when focusing on short term changes.

Knowledge of the short term course is relevant, for example to determine the best moment to intervene, and to evaluate the effect of emerging treatments. Therefore, the goal of this study was to scrutinize the short term disease course of DD in participants with primary disease (with different levels of severity). To our knowledge, no measurement exists to investigate this in participants. To this aim, we introduced surface area of nodules and cords as a new measurement to study disease course in participants without an extension deficit, and we studied the association between this measurement and the established classification of Tubiana.[17] We expect that several risk factors, such as age, gender, and age of onset, influence the course of disease. Thus, a secondary goal was to study the association between risk factors and short term disease course.

Methods

Study design and participants

In this prospective study, the study population comprised two groups of participants: first, people with DD who had not yet sought medical help, i.e. participants from the general population who were identified in a previous study on prevalence of DD in The Netherlands[11], and second, patients from a hospital population whom had been referred to us by their general practitioners because of their DD. In this study, only the results of primary affected hands were analyzed.

Measurements

This study focused on the detailed investigation of changes in the hands of participants with DD, measured at maximum intervals of six months during a period of 1.5 years. No methods exist to quantify changes in patients without an extension deficit. Therefore, we introduce a new way to study changes in these patients, namely measurement of surface area of nodules and cords in square centimetres with a tumorimeter[18,19] (PharmaDesign Inc., China). The inter-observer and intra-observer agreement on this measurement is high.[20] In addition to measurement of surface are, the passive extension deficit (PED) of each MCP, PIP and/or DIP joint was measured with a goniometer and added to form TPED, but only recorded when DD was present in this particular ray. Afterwards, the severity

of disease was categorized based on Tubiana's classification.[17] This classification per ray uses the TPED of finger joints: stage 0 = no apparent lesions; stage N = nodules without extension deficit; stage I = 1–45°; stage 2 = 46–90°; stage 3 = 91–135°; and stage 4 >135° TPED.

In addition to examination of the hands, participants were interviewed about potential risk factors for DD. Exposure to vibration included for example questions about playing tennis or field hockey, and occupational exposure to vibrating tools. Besides, we studied the presence of ectopic lesions by asking males about symptoms of Peyronie Disease, examining the hands for knuckle pads, and the feet for Ledderhose Disease when a participant had noticed plantar nodules. All measurements were performed by the first author, and with the same set of instruments during all moments of follow-up.

Statistical analyses

The population characteristics were described by means and standard deviations or by proportions with 95% confidence intervals, which were calculated using the *F* distribution.[21] Differences between the two populations at baseline were tested with Fisher's exact test (two-sided) for nominal variables, and with independent samples t-test for normally distributed continuous variables. Differences between non-normal distributed continuous variables were tested with Mann-Whitney *U* test.

To investigate the reliability of our surface area measurements, we studied whether there was an association between area and Tubiana stage at baseline. This was tested with generalized estimating equations (GEE), using the cumulative logit link function; an independent working correlation matrix; the robust estimator; and the generalized score statistic.[22] Hand and finger effects were considered within-subject variables in this analysis, so the results are applicable to all fingers of both hands.

To study disease course, we first focused on all changes (including minimal change) in surface area and extension deficit (if present). To obtain a mean change for the patients a linear mixed model for each finger separately was used. In this analysis a random intercept for cases was included, and the maximum likelihood method was used.[23] In addition, we used latent class models[24] for each finger separately to cluster changes in surface area (in all fingers) and TPED (only for ring and little finger). The number of clusters were determined by the Bayesian Information Criterion (BIC) with the restriction that no cluster would contain less than two subjects. We studied whether well-known typical risk factors for DD had an effect on short term change by testing a difference in these risk factors for the observed clusters. We used logistic regression for binary risk factors (gender, diabetes, epilepsy, liver disease, Peyronie disease, Ledderhose disease, knuckle pads and population), and linear regression for continuous variables (age at baseline). The significance level for all analyses was set at $\alpha = 0.05$.

Results

In total, 247 participants with 370 primary affected hands with DD were studied. In Table 1 population characteristics are listed. The majority of participants was male, and mean age of participants was 69.3 years (SD 9.1) for the general population and 63.8 years (SD 9.6) for the hospital population ($t(245) = 4.6$, $P < 0.001$). Mean age of onset reported by participants was 59.8 years (SD 10.7) and 53.8 years (SD 11.4) for the general population and the hospital population respectively ($t(196) = 3.7$, $P < 0.001$). Forty-nine participants could not remember their age of onset. Participants were asked whether they were exposed to vibration, and the vibration intensity was calculated as exposure in hours per week multiplied by number of years. The median vibration intensity was 125 (IQR 32.5–296.3) and 60 (IQR 29.9–216.6) for the general population and the hospital population respectively (Mann Whitney *U* test; $P = 0.416$).

Most participants were measured three or four times during 1.5 years, and one participant was measured for seven times with approximately 3 months between each measurement. In Table 2 the distribution of Tubiana stage for all moments of follow up is shown. Most rays were affected with nodules or cords, and a contracture was present in 15.9% of the affected rays (6.7% in general population and 23.6% in hospital population).

In Table 3, the median surface area and TPED per ray for the follow up moments (measurement 1-4) for most participants are shown. The ranges of the surface area and TPED were broad, indicating a large variation between participants.

With GEE, a significant association between surface area of DD and Tubiana stage was found ($P < 0.001$; OR 3.24; 95% CI 2.55–4.13). This means that for each square centimeter increase of surface area, the predicted odds of being in the highest category (Tubiana 4) versus the other categories is increased by a factor of 3.24.

Table 1. Population characteristics.

	General population N (%)	95% CI	Hospital population N (%)	95% CI	P-value
Participants	107 (43.3)	-	140 (56.7)	-	-
Females	49 (45.8)	36.1–55.7	40 (28.6)	21.3–36.8	0.007†
Family history of DD	34 (31.8)	23.1–41.5	66 (47.1)	38.7–55.6	0.018†
Ectopic lesions					
Knuckle pads	20 (18.7)	11.8–27.4	38 (27.1)	20.0–35.3	0.132
Peyronie Disease*	4 (6.9)	1.9–16.7	14 (14.0)	7.9–22.4	0.204
Ledderhose Disease	7 (6.5)	2.7–13.0	18 (12.9)	7.8–19.6	0.136
Diseases					
Diabetes	15 (14.0)	8.1–22.1	17 (12.1)	7.2–18.7	0.705
Epilepsy	2 (1.9)	0.2–6.6	1 (0.7)	0.02–3.9	0.580
Liver disease	1 (0.9)	0.02–5.1	1 (0.7)	0.02–3.9	1.000
Hand trauma					
Hand injury	42 (39.3)	30.0–49.2	76 (55.1)	46.4–63.5	0.103
Manual labor	40 (37.4)	28.2–47.3	44 (31.4)	23.9–39.8	0.345
Exposure to vibration	32 (30.8)	22.1–40.6	52 (38.2)	30.0–47.0	0.275
Life style factors					
Alcohol intake in glasses per week					
None	26 (24.3)	16.5–33.5	16 (11.4)	6.7–17.9	0.066
1-5	40 (37.4)	28.2–47.3	47 (33.6)	25.8–42.0	
6-10	17 (15.9)	9.5–24.2	26 (18.6)	12.5–26.0	
11-15	10 (9.3)	4.6–16.5	29 (20.7)	14.3–28.4	
16-20	7 (6.5)	2.8–13.0	13 (9.3)	5.0–15.4	
> 20	7 (6.5)	2.8–13.0	9 (6.4)	3.0–11.9	
Smoking					
Never	31 (29.2)	20.8–38.9	41 (29.3)	21.9–37.6	0.993
>1 year quitted	60 (56.6)	46.6–66.2	80 (57.1)	48.5–65.5	
<1 year quitted	1 (0.9)	0.02–5.1	2 (1.4)	0.2–5.1	
Current	14 (13.2)	7.4–21.2	17 (12.1)	7.2–18.7	

95% CI; 95% confidence interval. † Statistically significant difference calculated with two-sided Fisher's exact test.* Only applicable in males.

On average, the surface area and TPED increased slightly over time. The mean slope per day for all fingers was 0.0006 for area and 0.015 for TPED, which means that in one year, the mean area increases with 0.22 cm^2, and the mean TPED with 5.5 degrees. However, there was a large variance in change of surface area and extension deficit between individuals.

Table 2. Severity of disease

Tubiana stage	General population Number of rays	General population Percentage of affected rays	Hospital population Number of rays	Hospital population Percentage of affected rays	Total Number of rays	Total Percentage of affected rays
0	1983	-	1698	-	3681	-
N	1317	93.3	1293	76.4	2610	84.1
1	80	5.6	339	20.0	419	13.5
2	15	1.1	45	2.7	60	1.9
3	-	-	7	0.4	7	0.2
4	-	-	8	0.5	8	0.3

Table 3. Median area of DD and mean TPED per ray for measurements with the most participants from general and hospital population

Measurement	General population Median area in cm^2 (IQR)*	General population Median TPED (IQR)**	Hospital population Median area in cm^2 (IQR)*	Hospital population Median TPED (IQR)**
1	0.9 (0.5–1.6)	15.0 (10.0–30.0)	1.5 (0.8–2.7)	20.0 (10.0–32.5)
2	1.1 (0.6–1.7)	13.5 (10.0–43.3)	1.5 (0.8–2.7)	20.0 (10.0–31.5)
3	1.1 (0.7–1.9)	15.0 (10.0–39.5)	1.5 (0.8–2.7)	16.0 (10.0–30.0)
4	1.0 (0.6–1.8)	24.0 (9.5–41.0)	1.5 (0.8–2.6)	16.0 (9.5–28.5)

* Rays without DD were excluded, ** Rays without extension deficit were excluded.

The large variance between participants complicated the analysis on minimal changes of DD. Therefore, we studied with a latent class model whether clusters in change profiles were present. We found three to six different clusters per finger on change in surface area (Figure 1). The figure shows for each finger that not only increase, but also decrease and stability of disease can occur on average in respectively 5.1–42.8%; 11.1–40.2% and 44–75% of the patients. With respect to change in TPED fewer clusters were found. In Figure 2, the course is shown for the ring finger and the little finger, since for the other fingers not enough data was available. In the left ring finger, and the right ring and little finger three clusters are formed; one cluster that increases fast, a second cluster that remains fairly stable, and a third cluster that shows regression over time. In the left little finger the cluster which regresses is not present.

We studied whether the disease course was influenced by one or more risk factors (Table 1), but none of these variables could explain the variance in short term disease course or the presence of different clusters. Only surface area at baseline was identified as a predictor for the clusters on surface area in all fingers,

except the index finger. This means that participants with a smaller surface area at the start of the study were more likely to be in the regressive cluster. For TPED this association could not be proven.

Discussion

The aim of this study was twofold: first, to systematically investigate the natural course of DD over time in short increments; and second, to study the association between potential risk factors and this short term disease course. Furthermore, we introduced a new measurement to study disease course in early-phase DD.

To investigate whether our new measurement of surface area was related to disease severity, we studied the association between the surface area of DD and Tubiana stage. The results show that participants with a larger surface area of DD were prone to have a higher Tubiana stage. Therefore, we believe that measurement of the surface area is suitable to evaluate disease severity in participants without extension deficit, especially since the intra- and inter-observer agreement of this measurement is high.[20] To our knowledge it is the first time that exact measurement of surface area is used as outcome parameter in a study on DD.

In analyses on disease course we firstly studied changes in surface area and TPED over time, including very small changes. On average, the area of DD and extension deficit increased only slightly in one and a half years. However, there was a large variance in the short term course between individual participants. A part of this variance could have been caused by measurement errors. However, this effect was expected to be small, since all measurements were performed by the first author, and it has been shown that the intra-observer agreement on measurements of area and TPED is high.[20,25]

Secondly, we identified different clusters in the short term disease course based on surface area and TPED. The number of clusters differed per finger, and especially for the clusters in the ring fingers, it could be discussed whether the clusters that remain fairly stable should be seen clinically as separate clusters, or that these clusters could be merged. The BIC indicated that there are statistical differences between the clusters. Nonetheless, it is important to note that, during the 1.5 years of follow up, the disease was stable in most participants, but that also progression, regression and some fluctuation of disease can occur. We found an increase of surface area in 5.1–42.8%, however, a minimum increase of two cm^2 in area of DD was seen in less than 10% of the participants. In studies on long term

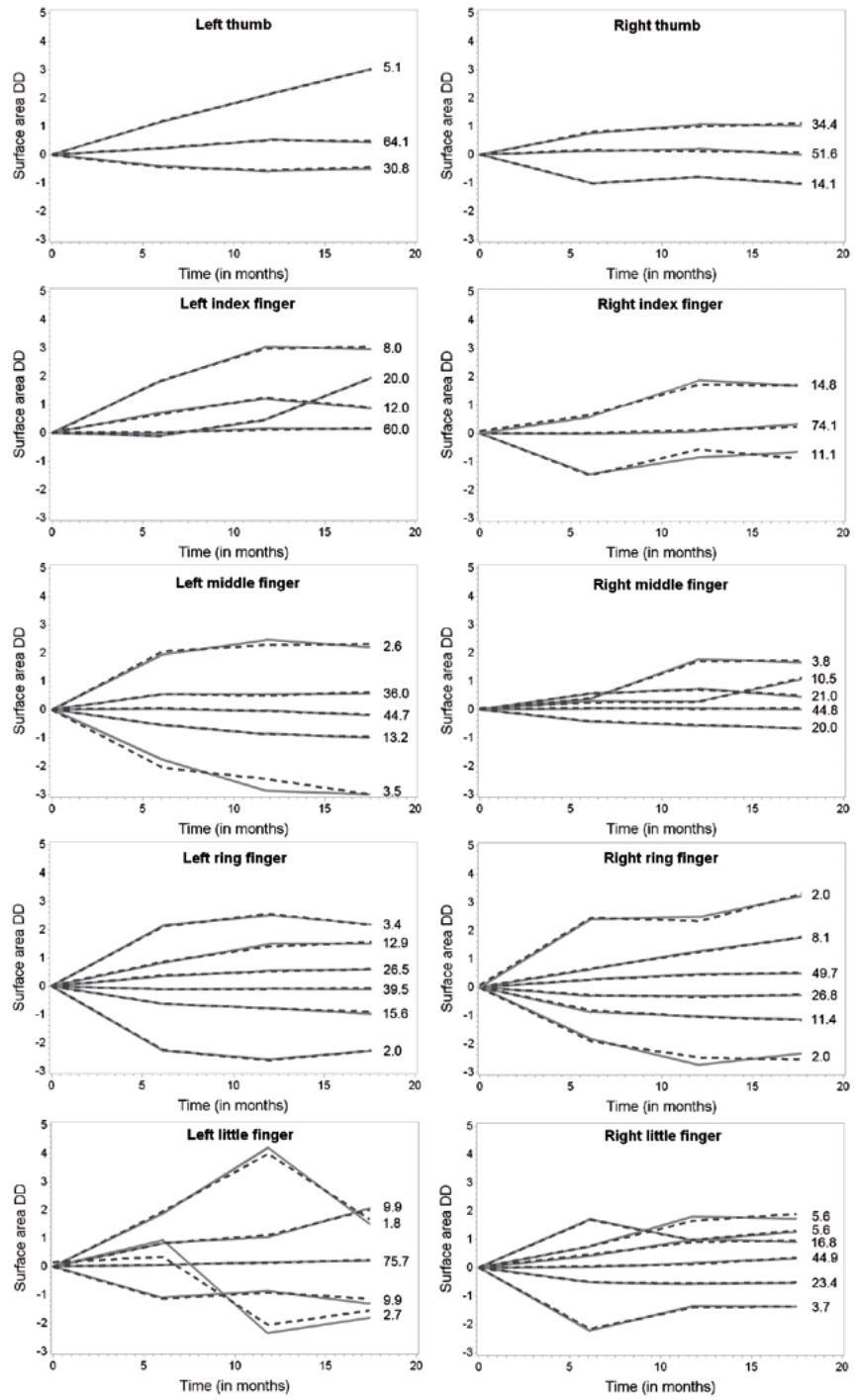

Figure 1. Clusters of change in surface area in cm^2. In this analysis surface area was subtracted with baseline surface area so that every participant starts at zero. The figure shows percentages of patients in each cluster with increase, decrease, fluctuation and stability of disease in different fingers. Solid line: observed values, dotted line: predicted values.

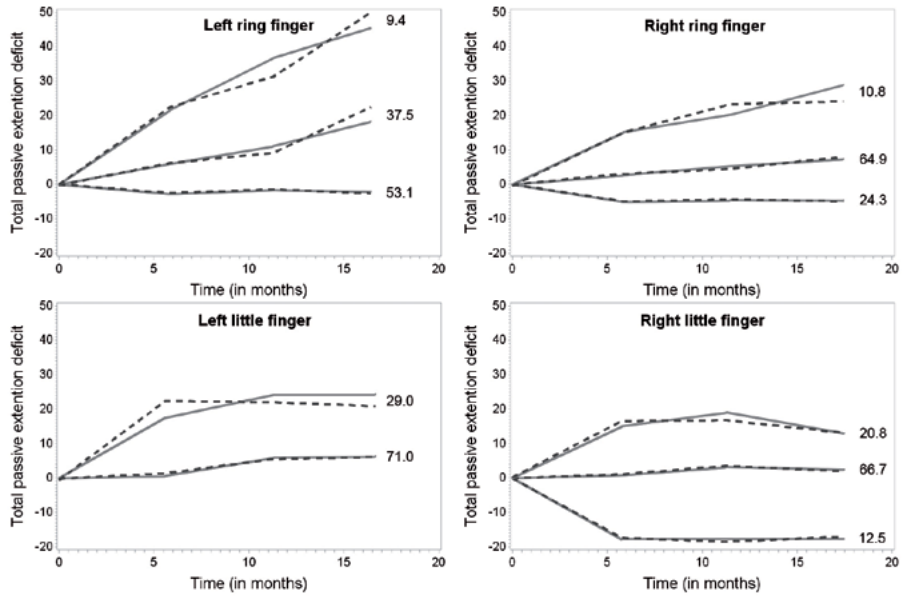

Figure 2. Clusters of change in total passive extension deficit (TPED) in degrees. The change is shown for the ring finger and the little finger, since for other fingers not enough data was available. The figure shows percentages of patients in each cluster with increase, decrease, and stability of disease in different fingers. Solid line: observed values, dotted line: predicted values.

disease course, higher progression percentages were seen, ranging between 34% and 51%.[13,14,26] Notwithstanding this, Reilly et al. also noticed stable disease or even regression in almost 50% of patients.[13]

Since no clear short term disease course could be identified, it was not possible to associate risk factors with disease course. Moreover, the population that participants originated from was not associated with differences in disease course. In studies on long term disease course, only European ethnicity and age of onset younger than 50 years were reported as predictors for disease progress.[13,14] However, we noticed that it is challenging for participants to remember their age of onset, so the predictive power of this variable should be interpreted with cause. With respect to different clusters in disease course of surface area, the area at the start of the study was the only variable that was associated with these clusters. In addition, surface area was strongly positively associated with Tubiana stage. Patients that are referred to the hospital usually have more advanced disease, i.e. a higher Tubiana stage with a larger surface area of DD. Therefore, it could be expected that these patients are more likely to be in the cluster with progressive disease. This could explain why clinicians, who especially care for these patients

with more advanced DD, have the impression that DD is always progressive. On the contrary, participants with Tubiana stage 1 or higher did not all show progression, and a substantial amount of patients improved.

Our results could influence the conclusions drawn from studies in which patients with nodules and cords without contractures were treated. For example, radiotherapy has been found to be effective to prevent disease progression of early stage DD.[27,28] Especially on short term follow up, patients who received radiotherapy showed no progression or even remission of disease. Our results show that this could be explained by the natural disease course of DD. Furthermore, long term results after radiotherapy show progression of disease in 31% of the treated hands[28], which is in line with the long term progression rates of untreated patients in previous studies and our results.[13,14]

One of the strengths of this study is the large number of participants with 370 primary affected hands. Furthermore, almost all participants originate from the Northern Netherlands, which enlarged the homogeneity of the study population.[1] In studies with only participants from a hospital population, usually mostly males are included in the sample.[29-31] Due to our method of selecting participants, we included a larger number of females than in most clinical studies, and the mean age was somewhat higher.[32] Furthermore, knuckle pads were seen in more participants[32], which could have been caused by difficulties with distinction between knuckle pads and dorsal cutaneous pads.[33] Nonetheless, we believe that our sample with a mixed population gives a broad insight to the natural course of DD.

A limitation of this study is that we used non-validated instruments; however, we used the same instruments for all measurements. Besides, in clinical practice many different goniometers are used that are not validated either. Furthermore, our data on risk factors are participant reported. This enlarges the risk of recall bias, especially regarding the variables age of onset, hand injury and exposure to vibration. To address this limitation, we interviewed all participants at every measurement and used the average of the answers in the current analyses.

This study on natural disease course of DD shows that, on short term, the disease is stable in most participants, especially in early-phase DD, but that also progression and regression of disease occurs. This knowledge contributes to the evaluation of short term results of non-invasive treatments. Furthermore, it can affect the design of new studies, since it is clear that longer follow-up is needed to

study the effect of treatment beyond the variance in short term disease course. In order to study the periods of activity and inactivity as seen in histological studies[12,15] more thoroughly, a continued follow up of our cohort is necessary.

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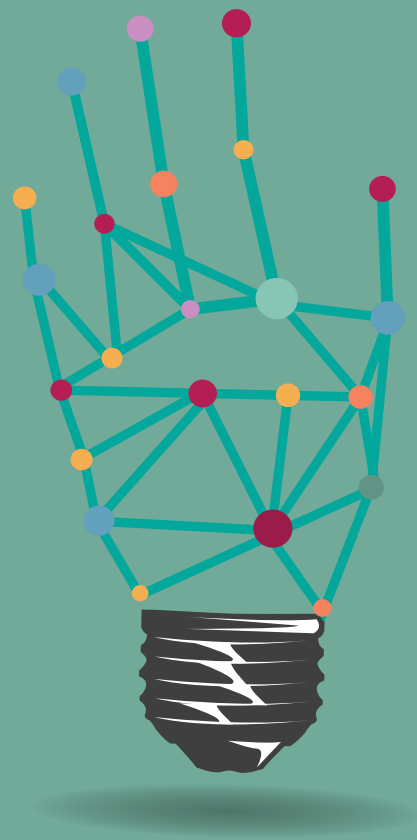

General discussion and future perspectives

Chapter 7

Dupuytren Disease is at present an incurable chronic disease that is treated symptomatically, and currently there are no possibilities to cure or prevent DD. In recent years, the focus of research was on genetics, cell and molecular biology, and treatment of DD. First, in the field of genetics, a major breakthrough was Dolmans et al.'s discovery of the genetic origin of DD.[1] Thereafter, a limited number of studies has been published on this topic and we are waiting for the succession of this research and the clinical implications.[2-5] Second, in cell and molecular biology, studies have focused on the myofibroblast, which is the cell deemed responsible for the expression of the disease. Furthermore, factors were studied that stimulated or inhibited myofibroblast contraction, such as matrix metalloproteases (MMPs).[6] Among others, it has been shown that tumor necrosis factor (TNF) promotes differentiation from fibroblasts into myofibroblasts, and that adipose-derived stem cells can inhibit proliferation of the myofibroblast.[7,8] This knowledge about TNF may offer entry points for future treatment of the disease. Currently four treatments are mostly performed in DD: dermofasciectomy, limited fasciectomy, percutaneous needle fasciotomy, and injection with collagenase *Clostridium histolyticum*.[9] They all have benefits and drawbacks that have been studied extensively.[10-16] However, the perfect treatment for DD has yet to be discovered.

Notwithstanding the efforts that are being made by all researchers in the field, there are still many aspects unknown, which, if revealed, will contribute to a better understanding of the disease. This includes prediction of the prevalence of DD, preferably based on the presence of risk factors; and second; foreseeing in which phenotype DD will occur in patients, i.e. which patterns exist in combinations of affected fingers. Third, once the disease has emerged, it would be an accomplishment to predict a patient-specific disease course over time, based on specific factors that are associated with this course. Ultimately, if the results of these and other studies can be combined, then the ability is near to define who should be treated and at what moment in time, and which treatment is the best patient-specific choice.

This thesis was designed to contribute to these aspects that previously did not receive sufficient attention and focused on gender specific and age-related prevalence rates. This thesis also introduced a new measurement method for early DD; and meticulously studied disease patterns and the short term course in DD. The findings and their implications will be outlined and put into perspective below.

Studies on the prevalence of Dupuytren Disease and risk factors in the general population

Prevalence of DD has been the subject of numerous studies in the last 50 years, however, data was lacking from the general population in The Netherlands. In Chapter 2, we studied this prevalence of DD in The Netherlands and found it to be as high as 22.1% in patients of over 50 years of age. In our random sample of the general population of Groningen, the number of patients with contractures or with recurrent disease was relatively low (18.9% and 4.1% of affected participants, respectively) when compared to the experience of surgeons active in the field, who mostly see patients with extension deficits and/or recurrent disease.[17,18] The question rises whether we have been looking at a different population than the one seen by surgeons, or that we have studied very early disease in patients from the same population.

In favor of the first theory is the study by Rayan that has suggested that two forms of DD can be distinguished: a form with a late age of onset and a mild course, not necessitating treatment, and a more aggressive form that develops at younger age and requires (repeated) treatment.[19] We calculated that the median age of our sample was 62 years, which is in line with the mean age at which most referred patients have their first treatment.[20] This indeed suggests that the aggressive form that requires treatment develops at a younger age, and that surgeons see a selected population which is not comparable to a random sample of the general population. However, the second theory is supported by the fact that a large part of the participants with DD had not noticed the disease at all by themselves, or that it was so mild that it did not worry them and therefore did not (yet) lead to a visit to the general practitioner, nor referral to a surgeon. With our prevalence study, we were unable to fully clarify whether different populations exist; however, the results from our study on disease course, which will be outlined below, did not show differences based on population.

The study on prevalence of DD was combined with investigating the role of certain risk factors, and we found a statistically significant association between DD and age, male gender, alcohol consumption of more than 15 units per week, family history of DD, and presence of Ledderhose Disease (Chapter 2). Using these risk factors, we developed a model that predicts the prevalence of DD at different ages with the presence or absence of these risk factors. This model contributes to the understanding of the occurrence of the disease, and enlarges knowledge of the

attribution of the different risk factors. It brings us a step closer to predicting the occurrence of DD.

In the graphs of the prediction model, the prevalence curves increase with age. However, in the highest age categories, there is a slight decrease in predicted prevalence. It has been stated that patients with DD, especially patients with a contracture or patients that have been operated on, live shorter than their controls, although the underlying cause has not been fully clarified, since not all studies corrected for confounders such as smoking.[21-23] Gudmundsson et al. found that patients with DD contractures had a significantly increased total mortality compared to participants without DD, and a higher cancer mortality (but not significant), when corrected for age and smoking habits.[22] Nine different genetic loci—that include genes involved in the Wnt-signaling pathway—play a role in the development of DD.[1] Changes in this Wnt-singnaling pathway influence cell proliferation and survival.[24] Other diseases that have been linked to abnormalities in the Wnt-signaling pathway include leukemia[25,26], a high bone mass (sclerosteosis)[27], pulmonary fibrosis[28], hair follicle tumors[27], and colon cancer[27,29,30]. It has yet to be proven that these diseases are linked to DD, and that the presence of such co-morbidities causes an increased mortality rate in patients with DD.

The prevalence of DD in The Netherlands is somewhere in the middle of the current reported prevalence rates of 0.2-56%, as published by Hindocha et al.[31] Since this range of reported prevalences is very broad, we decided to perform a systematic review and meta-analysis on the prevalence of DD in Western countries, and we were able to reduce the range to 0.6-31.6%. This range still is broader than we had expected. Systematic reviews and meta-analyses on the prevalence of other diseases also reported broad ranges. This was often caused by differences in the included studies regarding study design, population, diagnostic criteria, and geographic differences.[32-34] Although our inclusion and exclusion criteria were strict, we could not completely rule out heterogeneity in study design, population and geographic location as well. With respect to the latter, it has been suggested that DD is more common in the Northern countries because of hand exposure to low outside temperatures, which leads to vasoconstriction in the hands. This may result in local ischemia, which—after reoxygenation—may cause the formation of oxygen free radicals that have been found to play a role in the development of DD.[35] We question this theory because hypothermia is a very effective way to preserve natural scavenging systems in tissues, and thus prevents the deleterious effects of ischemia and subsequent reperfusion.[36-38] To elucidate the role of geographic location, we studied the association between mean outside temperature in several countries and prevalence of DD. To this end, we added geographic location to the generalized linear mixed model from our meta-analysis (Chapter 3). We plotted the random differences between the geographic locations to study an order in these locations; however, this did not demonstrate a clear trend. Figure 1 shows, regarding studies from England, that for males the prevalence found by both Bennett[39] and Burke[40] was lower than the median prevalence from the meta-analysis, while the prevalence from Arafa[41] was higher than the median, although the geographic locations are not that different. This inconsistency shows that it is difficult to draw conclusions about the relation between prevalence of DD and geographic location.

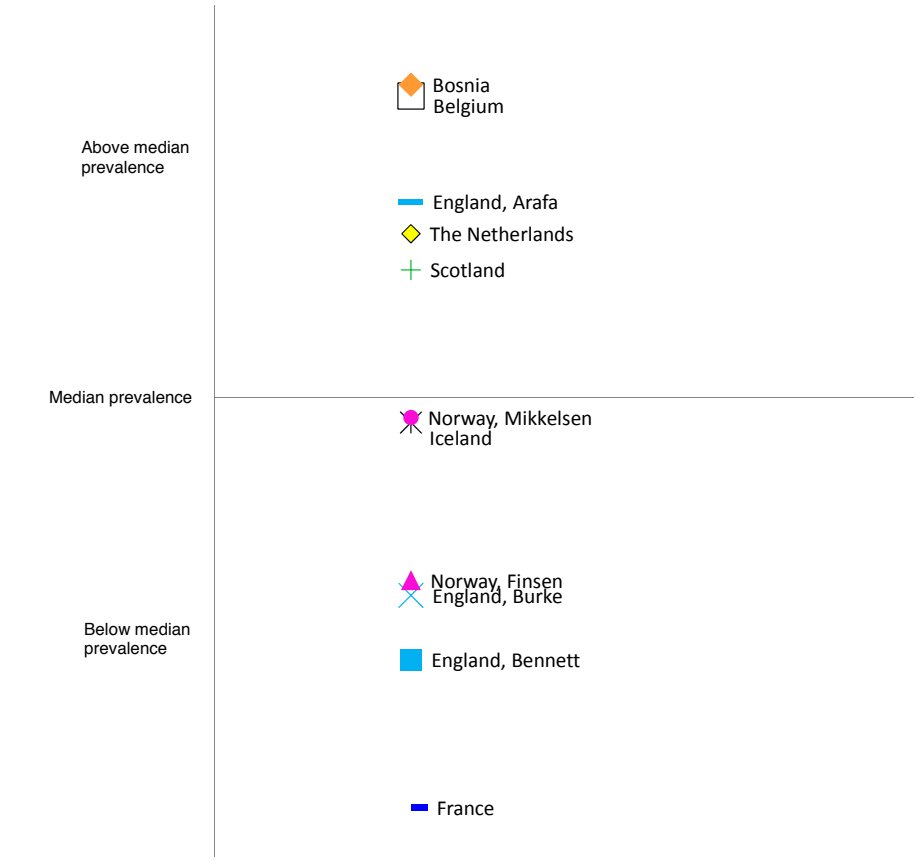

Figure 1. Relative distance of prevalence in different geographical locations to the median prevalence of males in the meta-analysis from Chapter 3. The greater the distance to the baseline, the further the prevalence deviates from the median prevalence.

The difficulties that we experienced in explaining the association between prevalence and geographic location could imply that either our approach was not correct, or that the data were not suitable to be analyzed. Comparatively, in other diseases such as multiple sclerosis and IgA nephropathy, the differences in prevalence distribution are based on genetic variation, differences in environment, and their interaction.[42,43] In multiple sclerosis, demographic epidemiology has changed in the past decades; prevalence has increased due to longer survival, and more women are affected, probably through a change in female lifestyle.[42] In IgA nephropathy, variation at genetic susceptibility loci is correlated to differences in disease prevalence among populations, and nearly 5% of the variation in disease risk could be explained by this genetic susceptibility.[43] As stated before, it has recently become apparent that nine genetic loci are associated with DD[1], and that some patients carry more risk alleles than others.[44] In line with multiple sclerosis and IgA nephropathy, it is possible that differences in demographic epidemiology and genetic susceptibility also account for a part of the differences in prevalence rates of DD.

Measurements of disease severity in Dupuytren Disease

In order to study disease patterns and the natural disease course of DD accurately, it was essential to use a classification that covers all stadia of DD in a suitable manner. Different classifications exist to categorize the severity of DD. Most of these classifications focus on extension deficit of the fingers[46-49], and patients with a contracture of the fingers are divided into three or four categories, while patients without an extension deficit are all merged into one category. However, as shown in previous studies[50,51] and confirmed by the results of Chapter 2, the general population has a low rate of patients with contractures, which makes these classifications less suitable for studies in this population without contractures.

For patients with only palmar disease, no standard measurement method existed to indicate disease severity. In previous studies, marking nodules and cords was used to assess the effect of radiotherapy in patients with early DD.[52,53] However, it is unclear how the exact treatment effect was measured since only "regression", "progression", or "status idem" were determined[54], without reporting whether measurement of the actual size of nodules and cords was performed.[53,55] This makes it difficult to interpret the exact effect of radiotherapy in early DD.

In Chapter 4, we have introduced the measurement of surface area as a new parameter of disease expression in patients without an extension deficit. Both intra- and inter-observer agreement of this measurement was high, and in Chapter 5 we have shown that there is a strong association between surface area and Tubiana stage. It should be noted that in patients with advanced disease, drawing and measuring the surface area becomes rather cumbersome and time-consuming. However, we showed that even someone without experience in diagnosing DD is able to accurately diagnose and measure DD after a relatively short training. Therefore, we believe that this new measurement is very useful to quantify change of disease in patients without an extension deficit, both in scientific research as well as clinically since it helps a surgeon to objectively determine disease progression.

In patients who, in addition to palmar disease, experience a contracture of one or more fingers, goniometry is used to measure the severity of the disease. The severity of a contracture is commonly used as an outcome measurement for recurrence after treatment, although, no clear definition of recurrence currently exists.[56] Furthermore, the measurement of contractures has been reported in numerous different ways, including "total flexion deformity"[53], "degrees of flexion"[57], "degree of extension lag"[58], "active extension loss"[59], "total extension deficit"[60], and "total passive extension deficit"[20]. This variety in reporting measurements of a contracture complicates comparison of the results, and moreover, the reliability of these measurements has not been studied thoroughly.

Therefore, in addition to agreement on measuring surface area, we studied the agreement in the determination of total *passive* extension deficit (TPED). This was the first study that investigated both intra- and inter-observer agreement of TPED in patients with DD. Previously, only one related study was performed regarding the reliability of measuring the *active* extension deficit. However, this study comprised a very small sample of 13 patients with DD, and only interrater reliability was investigated, which was found to be 0.949 for total active extension.[61] Our results, derived in a large sample of 54 patients, show that also *passive* measurement of the extension deficit has a high intra- and inter-observer agreement. Although the total active extension deficit (TAED) might correspond better with the patient reported disability, it is conceivable that the result of this measurement is dependent on the ability of the patient to powerfully extend the fingers, as well as on the evaluation of the investigator. When measuring passive extension deficit, the result is only dependent on the measurement of the investigator. Therefore, in our opinion, it is favorable to study passive extension deficit in patients with DD.

Disease patterns in Dupuytren Disease

Prior to studying the disease course of DD, we felt the need to study disease patterns in primary disease thoroughly. In other conditions, disease patterns are of interest to predict outcome or disease course as well. For example, in dermatology it is used to study development of naevi[62], in pulmonology to study the development of chronic thrombo-embolic pulmonary hypertension after pulmonary thrombo-embolism,[63] and in neurology, patterns of brain atrophy are used as marker for cognitive decline in patients with Parkinson's disease[64].

Regarding disease patterns in DD, several empirical articles—without firm statistical analyses—have been published. From these articles it has been deduced that the ring finger and little finger are correlated in DD, and that an affected radial side is accompanied by more severe disease in the ulnar side of the hand.[46,65-67] In Chapter 5, we studied in detail the presence of disease patterns, and tested these assumptions. In our cohort, most often one or two fingers were affected, and DD in all five fingers simultaneously was rare. Taking into account age and gender, the following fingers were correlated regarding disease severity: thumb and index finger; middle finger and ring finger; and middle finger and little finger. No relation could be proven between severity of DD and age and gender, although our results suggest that males and older patients have more severe disease. It has been reported that younger patients experience a more aggressive form of the disease and an earlier recurrence after treatment.[13] Our results lend support to the theory that patients with an aggressive form will have a more severe disease already at younger ages, since thereby the overall effect of age on severity will be reduced. The supposed correlation between the ring finger and little finger, and between the radial and ulnar side could not be confirmed, which is a new and valuable finding. It means that disease in the ulnar side is not a predictor for occurrence of DD in the radial side of the hand.

Our findings are important in the context of treatment and prevention. Since it is now clear that some fingers are correlated with respect to disease occurrence and severity, it may be wise to treat these fingers simultaneously. On the contrary, since there is no correlation between the ring finger and the little finger, our results suggest that it is justifiable to solely treat a contracture of the ring finger, even when a nodule or cord in the palm of the little finger is present as well.

Short term disease course in primary Dupuytren Disease

Dupuytren disease is known as a chronic disease, and is thought to be progressive over time, at least in many cases. However, until now, the disease course has been studied with one moment of follow up only,[57,59] and consequently, the exact course over time is not known. It is important to study disease course in DD, since the indication for (surgical) treatment is a MCP joint contracture of >30 degrees or a PIP joint contracture of >20 degrees with *documented progression*.[68]

We prospectively investigated the disease course with predefined intervals of six months in participants with primary disease (Chapter 6). For investigation of disease course in cases with only nodules and cords, but no contractures, we used our new measurement of surface area. To determine disease course of contractures, we analyzed changes in TPED.

The most important finding was that progression and regression of the disease occurs, but that overall, the disease is stable in the majority of patients during one and a half years of follow up. Furthermore, we showed that the variation in short term disease between cases was large (without being caused by measurement errors). These findings have very important clinical implications. Firstly, the findings could affect the conclusions derived from studies in which patients with early stage disease were treated for DD. For example, radiotherapy has been found to be an effective treatment for nodules in the proliferative stage.[54,55] On the short run, patients who received radiotherapy showed no progression or even remission of disease. Our results show that this could also be explained by the natural disease course of DD, and therefore, the results of these studies without a control group should be interpreted with caution. Secondly, our results can be very useful in the design of new studies since it is now clear that a prolonged follow-up is needed to study the effect of treatment beyond the variance in short term disease course, especially if it concerns the effect of treatment in patients with early-phase DD. Thirdly, it is disadvantageous to intervene too early, since there is a high rate of recurrence after treatment.[13] Knowledge of the natural disease course is of interest in relation to the moment of treatment because in case the disease is stable or even regresses after a while, treatment may not be necessary.

We studied whether certain risk factors could be linked to the differences in short term disease course. Only the size of the surface area at the start of the study could be linked to the different clusters in course of the surface area. No other associations were identified, which could be caused by the large variation in

disease course between cases. Besides, the study population has been subjected to selection bias, since patients with extensive disease or an aggressive disease course were operated on, and therefore dropped out of the study. As a consequence, particularly participants with mild DD will remain in the study, and the curve of progression will flatten. This makes it more difficult to find an association between disease course and risk factors. A third consideration might be that risk factors only play a role in the onset of both primary as well as recurrent disease, and that once the disease is present, disease patterns and disease course are no longer influenced by these external risk factors. Perhaps that increased knowledge about genetic risk profiles can provide clarity on this topic.

Strengths and limitations of this thesis

One of the strengths of this thesis is the cross-sectional and prospective design of our studies in which all participants were physically examined. This physical examination enlarges the reliability of our outcomes, especially compared to studies that collected data with questionnaires only.[69,70] Furthermore, our study samples are large in comparison to other studies regarding prevalence[71,72], agreement on measurements[61,73], and disease course[57,59,74]. Another strength is the use of extensive statistical analyses, in which particular attention was paid to the fact that most of our data is correlated. To our knowledge such analyses are not frequently used in studies on DD.

Several limitations of our research should be noted. In this thesis, the study populations of Chapter 2, 4, 5 and 6 are closely related. In our design and analyses, we have tried to control for bias and confounders. However, if any undetected selection bias was present in our population, this will have influenced several studies in this thesis. Furthermore, this study population originated from the northern Netherlands, and therefore it might not be possible to extrapolate our results directly to other parts of the world. Notwithstanding this specific population, our results regarding prevalence of DD and occurrence of DD among fingers are comparable to previous publications from Europe[50,65,66,72] and Japan[67].

In this thesis we focused on patients with primary DD, which causes selection bias, especially in relation to severity of disease. Most of our participants were affected with nodules and cords, but without contractures of the fingers. Therefore, our results might be less applicable to tertiary hospitals that mainly treat patients with severe primary disease or with recurrent disease after previous treatment.

Future perspectives

In Chapter 2 we studied the association between prevalence of DD and risk factors; however, it remains a challenge to pinpoint at associations within diseases that probably have a multifactorial origin. Furthermore, in a cross-sectional study it is not possible to determine a causal relationship, and therefore, a prospective cohort study would be a more suitable design for such research question. In the northern Netherlands, a large observational follow-up study called LifeLines is currently running, with 165,000 participants covering three generations.[75] If studying the occurrence of DD could be included in the measurements of LifeLines, the causal relationship between DD and previously supposed risk factors could be clarified. Preferably, this should be preceded by a systematic review of the literature and meta-analysis on this topic, to get an overview of the risk factors that should be taken into account, and to which extent these factors are expected to contribute to the onset of DD.

Based on the results of Chapter 4, we concluded that preferably the TPED should be used in patients with DD, instead of TAED. However, to substantiate this statement, and to make it possible to compare results of studies that use either TPED or TAED, it would be interesting to study the agreement between the active and passive measurement. For example, the TAED could be measured in patients who were all found to have the similar TPED. If active measurement is reliable, than the outcome of measuring the TAED should be comparable in all of these patients.

In Chapter 5, we studied the correlation between fingers on occurrence and severity of DD, and in this general discussion the potential implications for surgical treatment were discussed. However, before definite conclusions on this topic can be drawn, the correlation between fingers on progression of disease should be studied as well.

In chapter 6, the results on short term disease course were presented. For future research, this cohort should be followed for several years to investigate the long term disease course. In addition, the patient reported disability should be studied more extensively, which is especially important in our aging population with prolonged working life. Furthermore, in studies that focus on treatment outcome, occurrence of recurrence is often studied as an outcome parameter. It will be complementary to enhance our knowledge about the course of recurrent disease after different treatment modalities. Such study could facilitate the decision making process to choose the most favorable patient-specific treatment.

It has been shown that DD is a complex disease, and genetic factors play an important role in disease susceptibility.[1] These factors, for example genetic risk score based on the number of affected SNPs, should be taken into account in the previously mentioned future perspectives.

Conclusion

The studies in this thesis have contributed our knowledge about prevalence, measurements, disease patterns, and short term disease course of DD. If our results will be combined with the results of previous and future studies, we are closer to predicting the right treatment at the best time for each patient individually, and this is a step towards a cure for DD.

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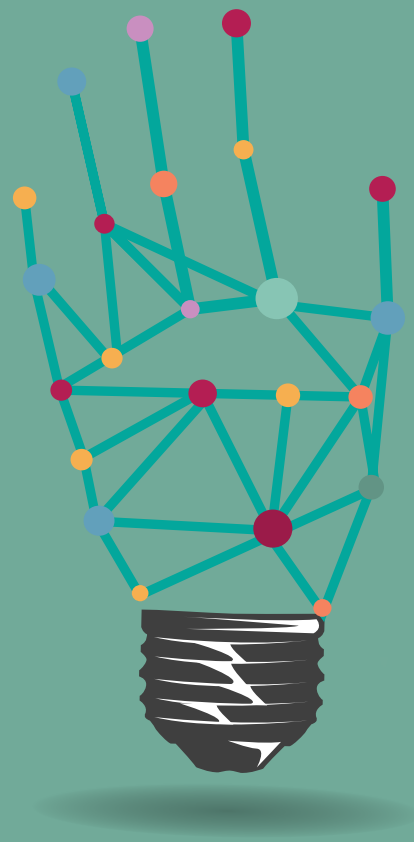


Summary and Samenvatting

Chapter 8

Summary

Dupuytren Disease (DD) affects the palmar fascias of the hand and fingers. At present, there are no possibilities to cure or prevent DD. Although numerous studies have been performed in the past decades, still many epidemiologic aspects about DD are unknown. This thesis was designed to contribute to these aspects and focused on gender specific and age-related prevalence rates. This thesis also introduced a new measurement method for early DD, and meticulously studied disease patterns, and the short term disease course in DD.

In **Chapter 2**, we found that the prevalence of DD is 22.1% in the general population older than 50 years of age in The Netherlands. Regarding the severity of disease, nodules and cords were seen over four times more often than contractures of the fingers. The prevalence of the disease increased with age, and males were more often affected than females. Other significant risk factors for DD include excessive alcohol consumption, previous hand injury, familial occurrence of DD, and presence of Ledderhose disease. With these significant risk factors, we developed a logistic prediction model that can be used to estimate the prevalence of DD in The Netherlands, based on the presence or absence of these risk factors.

Although the prevalence of DD has been studied extensively, an accurate description of the prevalence range in the general population—and of the relation between age and DD—was lacking. Accordingly, we performed a systematic review and meta-analysis on the prevalence of DD in Western countries and the association with age. In **Chapter 3** we present a prevalence range of 0.6-31.6% for DD in this population. Neither the quality nor the geographic location of the included studies could explain this wide range. In addition, we studied the relationship between age and prevalence for the total population and for men and women separately. With our results, it possible to predict the prevalence at a certain age in a healthy nonhospital population. Now that the population is aging, the results from **Chapter 2 and 3** can be helpful to medical doctors to estimate the growth of patient inflow. Furthermore, policymakers can use these graphs to evaluate the effect of DD on labor participation in an aging population.

In **Chapter 4** we studied the intra- and inter-observer agreement of four variables for diagnosing DD and its severity, namely: 1) the diagnosis itself; 2) Tubiana stage; 3) total passive extension deficit (TPED) measured with a goniometer; and 4) the area of nodules and cords measured with a tumorimeter. The latter is a new measurement variable that we introduced to study the disease in patients with early-phase DD. We studied the agreement of these four variables in 78 hands of 54 participants with primary DD. On average, the intra-observer agreement was slightly higher than the inter-observer agreement. Overall, the agreement on diagnosing DD and determining its severity was high. In addition, the newly introduced variable area of nodules and cords has a high intra- and inter-observer agreement, indicating that it is a suitable method to measure disease severity in early-phase DD.

DD affects fingers in a variable fashion, and knowledge about specific disease patterns based on location and severity of the disease was lacking. In **Chapter 5**, we showed that regarding severity of disease the following fingers are correlated: thumb and index finger; middle and ring finger; and the middle and little finger. This means that, for example, a more severe disease of the thumb is accompanied by more severe disease of the index finger. In our study, the previously supposed correlations between the ring and little finger, and between fingers from the ulnar and radial side of the hand, could not be demonstrated. This suggests that occurrence on one side of the hand does not predict DD on the other side of the hand.

The short term disease course of primary DD has been investigated in **Chapter 6**. In this study, we examined the hands of 247 participants with DD at intervals of 3-6 months, over the course of one and a half years. We studied the area of nodules and cords (as introduced in **Chapter 4**) as well as the TPED. The results show that the surface area is highly associated with disease severity based on Tubiana stage. Furthermore, on average the surface area increased with 0.22 cm^2 and TPED with 5.5 degrees per year; however, the variance between participants was large. The most important finding is that, with respect to change in surface area and TPED, different profiles in change were observed; progression of disease was seen, but also stability and even regression. Besides the surface area at baseline, no other variables could be linked to these differences in disease course.

The studies in this thesis have contributed to our knowledge about prevalence, measurements, disease patterns, and short term disease course of DD. If our results are combined with the results of previous and future studies, we are closer to predicting the right treatment at the best time for each patient individually, and this is a step towards a cure for DD.

Samenvatting

De ziekte van Dupuytren is een aandoening van de palmaire fascie van de hand en vingers. Op dit moment zijn er geen mogelijkheden om de ziekte van Dupuytren te genezen of te voorkomen. Hoewel er in de afgelopen decennia meerdere onderzoeken zijn verricht naar deze aandoening, zijn er nog veel aspecten van de ziekte onbekend. Dit proefschrift was erop gericht een bijdrage te leveren aan het vergroten van de kennis met betrekking tot deze onbekende aspecten en richtte zich ten eerste op geslachtsspecifieke en leeftijdgerelateerde prevalentie van de ziekte. Ten tweede hebben we een nieuwe meetmethode voor het beginstadium van de ziekte van Dupuytren geïntroduceerd, en ten derde de aanwezigheid van bepaalde ziektepatronen onderzocht. Ten slotte hebben we het natuurlijk beloop van de ziekte van Dupuytren op korte termijn in kaart gebracht.

In **hoofdstuk 2** hebben we ontdekt dat de prevalentie van de ziekte van Dupuytren 22.1% bedraagt in de Nederlandse algemene bevolking ouder dan 50 jaar. Met betrekking tot de ernst van de ziekte zagen we noduli en strengen meer dan vier keer zo frequent als contracturen van de vingers. De prevalentie nam toe met een stijgende leeftijd, en mannen hadden de ziekte vaker dan vrouwen. Overige significante risicofactoren die geassocieerd konden worden met de ziekte van Dupuytren zijn: overmatig alcoholgebruik, handletsel in het verleden, familiair voorkomen van de ziekte van Dupuytren en de aanwezigheid van de ziekte van Ledderhose. Met deze significante risicofactoren hebben we een logistisch predictiemodel ontwikkeld dat gebruikt kan worden om de prevalentie van de ziekte van Dupuytren in Nederland te schatten, gebaseerd op de aan- of afwezigheid van deze risicofactoren.

Hoewel de prevalentie van de ziekte van Dupuytren uitgebreid is onderzocht, ontbrak een accurate beschrijving van de spreiding van de prevalentie in de algemene bevolking, evenals de relatie tussen deze prevalentie en leeftijd. Om deze spreiding te verhelderen hebben we een systematisch review en een meta-analyse uitgevoerd, gericht op de prevalentie van de ziekte van Dupuytren in de algemene bevolking van Westerse landen en de associatie tussen prevalentie en leeftijd. In **hoofdstuk 3** presenteren we ten eerste een spreiding van de prevalentie van 0.6-31.6%. Deze spreiding kon niet verklaard worden door de kwaliteit van de studies of de geografische locaties waar de studies waren uitgevoerd. Ten tweede presenteren we de relatie tussen leeftijd en de prevalentie van de ziekte van Dupuytren voor de totale populatie, en voor mannen en vrouwen afzonderlijk. Met de resultaten van deze analyse is het mogelijk om de prevalentie van de ziekte van Dupuytren te voorspellen op een bepaalde leeftijd in een gezonde populatie. Nu de levensverwachting toeneemt, kunnen de resultaten van **hoofdstuk 2 en 3** door artsen gebruikt worden om de toename van nieuwe patiënten met de ziekte van Dupuytren in te schatten. Daarnaast kunnen de gegevens gebruikt worden door politici en beleidsmakers om het effect van de ziekte van Dupuytren op arbeidsparticipatie in een verouderende populatie te evalueren.

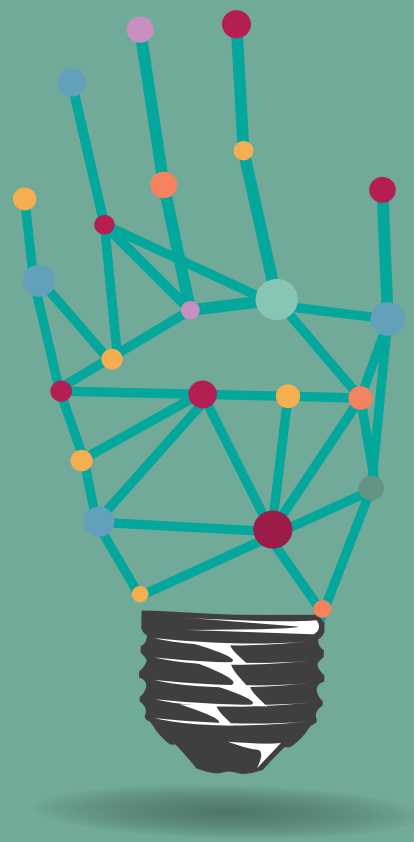
In **hoofdstuk 4** hebben we de intra- en interbeoordelaarsbetrouwbaarheid van vier variabelen onderzocht die gebruikt worden bij het stellen van de diagnose en het bepalen van de ernst van de ziekte van Dupuytren: 1) de diagnose zelf; 2) Tubiana stadium; 3) totale passieve extensiebeperking gemeten met een goniometer; en 4) de oppervlakte van noduli en strengen gemeten met een tumorimeter. Het meten van de oppervlakte van noduli en strengen in een nieuwe meetmethode die we hebben geïntroduceerd om de ziekte in kaart te brengen bij patiënten met beginnende Dupuytren zonder kromstand van de vingers. Van deze vier variabelen hebben we de overeenkomst tussen beoordelaars onderzocht in 78 handen van 54 patiënten met primaire ziekte van Dupuytren. De intrabeoordelaarsbetrouwbaarheid was in het algemeen enigszins hoger dan de interbeoordelaarsbetrouwbaarheid. De overeenkomst met betrekking tot het stellen van de diagnose en het bepalen van de ernst van de ziekte was hoog. Daarnaast was er een hoge overeenkomst in het meten van de oppervlakte van noduli en strengen. Dit bekent dat deze nieuwe meetmethode geschikt is om de ernst van de ziekte te bepalen in patiënten met beginnende ziekte van Dupuytren.

De ziekte van Dupuytren kan in verschillende vingers voorkomen en het was onbekend of er bepaalde patronen bestaan op basis van de locatie en de ernst van de ziekte. In **hoofdstuk 5** hebben we laten zien dat de ernst van de ziekte gecorreleerd is in de volgende vingers: duim en wijsvinger, middelvinger en ringvinger, en middelvinger en pink. Dit betekent dat bijvoorbeeld een ernstigere ziekte in de duim samen gaat met een ernstigere ziekte in de wijsvinger. In ons onderzoek konden we eerder gestelde correlaties tussen de ringvinger en de pink, en tussen de vingers van de radiale zijde en de ulnaire zijde van de hand, niet aantonen. Dit suggereert dat het optreden van de ziekte van Dupuytren in één zijde van de hand niet voorspelt dat er ook Dupuytren in de andere zijde van de hand optreedt.

Het korte termijn beloop van primaire Dupuytren is onderzocht in **hoofdstuk**

6. In dit onderzoek hebben we gedurende anderhalf jaar de handen van 247 patiënten met de ziekte van Dupuytren elke 3-6 maanden onderzocht. We hebben de oppervlakte van noduli en strengen gemeten (zoals geïntroduceerd in **hoofdstuk 4**) en de totale passieve extensiebeperking. De resultaten laten zien dat de oppervlakte sterk geassocieerd is met de ernst van de ziekte gebaseerd op het Tubiana stadium. Gemiddeld nam de oppervlakte met 0.22 cm^2 per jaar toe en de totale passieve extensiebeperking met 5.5 graden, echter de spreiding tussen patiënten was groot. De belangrijkste bevinding was dat er met betrekking tot verandering in oppervlakte en extensiebeperking verschillende profielen in verandering werden gezien. Er was toename van ziekte, maar ook stabiliteit en soms zelfs regressie van ziekte. Alleen de oppervlakte van noduli en strengen aan het begin van het onderzoek was van invloed op deze verschillen in beloop van de ziekte.

De studies in dit proefschrift hebben bijgedragen aan onze kennis over prevalentie, metingen, ziektepatronen en korte termijn beloop van de ziekte van Dupuytren. Als onze resultaten gecombineerd worden met de resultaten van eerdere en toekomstige onderzoeken, dan komt het voorspellen van de juiste behandeling op het beste tijdstip voor elke patiënt individueel dichterbij. Dit is een stap in de richting naar de genezing van de ziekte van Dupuytren.



Dankwoord

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jaren zal ik jullie niet meer lastig vallen met verhalen over statistische modellen, maar met sappige verhalen uit de kliniek. Hopelijk volgen er nog vele weekendjes met Puur, PuurPlus en PuurPlusMini's!

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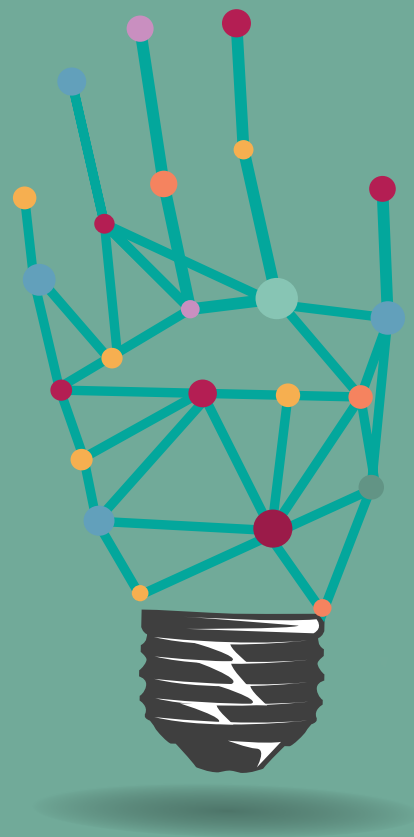
Lieve Harmen Jan, al tien jaar zijn we onafscheidelijk en je hebt me zien veranderen van een groene eerstejaars naar een gepromoveerde wetenschapper. Jouw Friese spreekwoord 'Pikerje net, it komt dochs oars' heeft mij als nuchtere Groningse vaak geholpen, met name toen er op het einde van mijn onderzoek nog een kleine verandering optrad met grote gevolgen. Ik verheug me op nog vele tientallen jaren samen met jou en onze Yfke!



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5. Lanting R, Van den Heuvel ER, Werker PMN
   Clusters in short term disease course in participants with primary Dupuytren Disease
   Submitted

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   Intra- and inter-observer agreement on diagnosis and measurements of Dupuytren Disease severity
   Submitted

Curriculum Vitae

Rosanne Lanting was born on November 22nd 1986 in Groningen, The Netherlands. After graduating from the Gomarus College in Groningen, she studied Medicine at the University of Groningen from 2005 until 2012. During the last year of her Master's she worked at the Department of Plastic Surgery at the University Medical Center Groningen (UMCG). Her master thesis, written under supervision of P.M.N. Werker, MD, PhD, comprised the prevalence of Dupuytren Disease. This was the foundation for her PhD thesis on Dupuytren Disease. After receiving a UMCG Junior Scientific Masterclass grant, she completed her thesis within two and a half years.

In December 2014 Rosanne will start her general surgery training at the Martini Hospital in Groningen. Thereafter, she will continue her Plastic Surgery residency at the Department of Plastic Surgery at the UMCG.

PhD Portfolio

Summary of PhD training and activities

Rosanne Lanting
University Medical Center Groningen, Department of Plastic Surgery
PhD period: February 2012 – July 2014
Promotores: P.M.N. Werker, MD, PhD and E.R. van den Heuvel, PhD

Courses

	Date	Credits
· Epidemiology and applied statistics	2011	3
· Projectmanagement	2012-2014	2
· Publishing in English	2012	2
· Medical Statistics	2013	3
· BROK-cursus	2013	1.5
· Applied Longitudinal Data Analysis	2013	1.5

Presentations

· Oral presentation at the biannual meeting of the Dutch Society of Plastic Surgery (NVPC) in Groningen, The Netherlands. Title: 'Prevalentie van de ziekte van Dupuytren in Nederland'	2012	0.1
· Lecture for the 'Medische Publieksacademie' of Dagblad van het Noorden and Menzis. Title: 'Koetsiershanden'	2013	1.0
· Oral presentation at the international annual meeting of the British Society of Surgery of the Hand' in Harrogate. Title: 'Prevalence of Dupuytren Disease in The Netherlands'	2013	0.5
· Oral presentation at the biannual meeting of the Dutch Society of Plastic Surgery (NVPC) in Amsterdam, The Netherlands. Title: 'Patronen in aangedane vingers bij de ziekte van Dupuytren'	2014	0.1

Supervising

Bachelor thesis

· Supervising BSc thesis by S.T Paaijens: 'Is there a pattern in the combination of Dupuytren affected fingers in one hand?'	2011
· Supervising BSc thesis by B. Skidmore: 'Prevalence of Dupuytren's disease in The Netherlands'	2011

Master thesis

· Supervising MSc thesis by B. Westerink: 'Prevalence of Dupuytren's disease in The Netherlands'	2011-2012	2.0
· Supervising MSc thesis by N.S. Kornmann: 'Phenotype in Dupuytren's disease'	2012	2.0

Seminars

· 'Publishing with impact: insights from the inside' by Dr. Meera Swami, Senior Editor of Nature in Groningen, The Netherlands	2012	0.1
· Biannual meeting of the Dutch Society of Plastic Surgery (NVPC) in Nijmegen, The Netherlands	2013	0.1
· International Bob Huffstadt conference 'Around the face' in Groningen, The Netherlands	2013	0.1

Other

· Reviewing of 2 manuscripts	2013	1.0