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Limited progression of subclinical Dupuytren's disease

RESULTS FROM A PROSPECTIVE COHORT STUDY

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Aims

With novel promising therapies potentially limiting progression of Dupuytren's disease (DD), better patient stratification is needed. We aimed to quantify DD development and progression after seven years in a population-based cohort, and to identify factors predictive of disease development or progression.

Methods

All surviving participants from our previous prevalence study were invited to participate in the current prospective cohort study. Participants were examined for presence of DD and Iselin's classification was applied. They were asked to complete comprehensive questionnaires. Disease progression was defined as advancement to a further Iselin stage or surgery. Potential predictive factors were assessed using multivariable regression analyses. Of 763 participants in our original study, 398 were available for further investigation seven years later.

Results

We identified 143/398 (35.9%) participants with DD, of whom 56 (39.2%) were newly diagnosed. Overall, 20/93 (21.5%) previously affected participants had disease progression, while 6/93 (6.5%) patients showed disease regression. Disease progression occurred more often in patients who initially had advanced disease. Multivariable regression analyses revealed that both ectopic lesions and a positive family history of DD are independent predictors of disease progression. Previous hand injury predicts development of DD.

Conclusion

Disease progression occurred in 21.5% of DD patients in our study. The higher the initial disease stage, the greater the proportion of participants who had disease progression at follow-up. Both ectopic lesions and a positive family history of DD predict disease progression. These patient-specific factors may be used to identify patients who might benefit from treatment that prevents progression.

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Introduction

Dupuytren's disease (DD) is a benign fibroproliferative disorder of the hand, characterized by the formation of fibrous nodules and cords in the palm and fingers. The condition can lead to flexion contractures of the hand that limit hand function and reduce quality of life.[1] To date, no curative treatment for DD is available. Current therapies (i.e. fasciectomy, needle aponeurotomy, and injection with collagenase clostridium histolyticum) aim to improve hand function by reducing joint contractures, yet these treatments are associated with moderate to high recurrence rates.[2,3] Current research is increasingly focused on novel therapies that aim to prevent or slow progression of early DD. Examples of these are local radiotherapy, intranodular injections of corticosteroids, and injection with anti-tumour necrosis factor.[4-6] Therefore, it is increasingly relevant to know which proportion of the affected population is susceptible to disease progression and which patient characteristics are relevant in estimating the risk of disease progression.

Only a few, relatively small studies have reported data on the natural history of DD. A prospective study by Lanting et al[7] that evaluated the short-term (1.5 years) disease course

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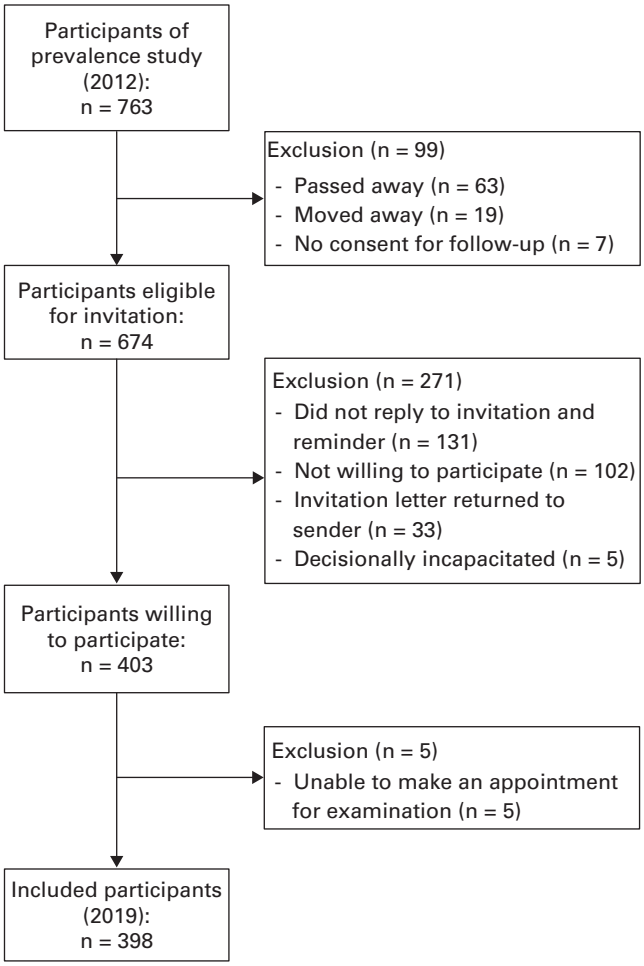

Fig. 1

Flowchart of the patient inclusion process.

concluded that DD is stable in most participants, especially in early-phase DD, but that both progression and regression may occur. Another study by Reilly et al[8] reported a high progression rate of 51% after only 8.7 years in a small hospital population of 59 patients. A third long-term follow-up study by Gudmundsson et al[9] involving 122 DD patients reported a progression rate of 38% after 18 years among a general population, but potential predictors of disease progression were not assessed. Increased knowledge on the course of DD is crucial to apply preventive therapies appropriately when they become available.

The aim of this prospective cohort study was to identify what proportion of DD patients who previously participated in a DD prevalence study had disease progression after seven years of follow-up, what factors are predictors of progression, what proportion of people previously being unaffected developed DD during seven years of follow-up, and what factors are predictors of development of DD.

Methods

Study population. A total of 763 individuals participated in a previous study on the prevalence of DD in the Netherlands in 2012.[10] The survivors were asked to participate again in our current cohort study. This fixed cohort includes subjects from the general population aged 50 years or older, who comprised a random sample of 1,360 individuals in 2012, drawn from the municipal administration of the city of Groningen, the Netherlands. From the original cohort of 763 participants, 398 (52.2%) were available and willing to engage in this follow-up study and could provide written informed consent (Figure 1). The clinical characteristics of this follow-up cohort of 398 participants are specified in Supplementary Table i.

Table I. Adapted Iselin classification of different stages of Dupuytren's disease.

Iselin stage	Clinical features
Stage I	Palmar nodules and small cords without signs of contracture
Stage II	Contracture of a MCP-joint or PIP-joint
Stage III	Contracture of a MCP-joint and PIP-joint in one finger
Stage IV	Contracture of the MCP-joint and PIP-joint with hyperextension of the DIP-joint

An adapted version of the Iselin classification has been used because the standard version does not cover the possible occurrence of an isolated PIP-contracture. In this study, an isolated PIP-joint contracture has been classified as stage II.
DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal.

Outcome measures. DD was diagnosed if the participant showed tethering or pitting of the palmar skin, nodules, cords, or joint contractures in the presence of a cord. A joint contracture was defined as the presence of an active extension deficit as a consequence of cord formation, assessed by visual estimation of the examiner. For the assessment of the severity of the disease, an adapted version of the Iselin classification was used (Table I).[11] The primary outcome measure was progression of DD. Progression was defined as advancement into a next disease stage at the time of follow-up in a subject with pre-existing disease, or when a subject had undergone surgical treatment for DD after 2012. To determine whether progression had occurred, participants were assessed for presence of DD, disease stage if DD was present and previous surgical treatment for DD. Secondary outcome was newly developed DD, which was defined as the presence of DD in previously unaffected participants.

During data processing, each participant was assigned to one Iselin stage to enable conclusions on a participant level (instead of finger level). If a participant was affected by DD in multiple rays the Iselin stage of the ray with the greatest change in Iselin stage was reported. Subsequently, all affected participants were assigned as having "progression", "stable disease" or "regression", according to a decision tree (Supplementary Figure a).

Predictors. The following variables have been evaluated as potential predictors for the occurrence or progression of DD: age, sex, diabetes mellitus, epilepsy, familial occurrence of DD, presence of ectopic lesions, manual labour, previous hand injury in one or both hands, excessive alcohol intake, and smoking status. All these variables were evaluated in 2012 and have been re-evaluated in the current study. In addition, we assessed variables that were not assessed in 2012: BMI, liver disease, medication for epilepsy, hypercholesterolaemia, hypertension,

Table II. Staging of Dupuytren's disease (DD) of the study cohort in 2012 and in 2019. Stable (disease) stage is highlighted in grey, progressive disease highlighted in blue, and regressive disease highlighted in red.

		2019						
		No DD	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Surgery**	**Total**
2012	**No DD**	249	52	4	0	0	0	305
	Stage I	6	63	11	0	0	2	82
	Stage II	0	0	1	3	0	1	5
	Stage III	0	0	0	0	0	3	3
	Stage IV	0	0	0	0	0	0	0
	Surgery	0	0	0	0	0	3	3
	Total	255	115	16	3	0	9	398

and familial occurrence of ectopic lesions (i.e. Peyronie's and Ledderhose's disease).

Study procedures. Information about the presence of DD was gathered by physical examination of the hands during home visits. The examinations in 2019 were carried out by one examiner, who was blinded for the findings of 2012. The examiner (BB) is a medical doctor experienced in investigating DD. One of the senior authors (DB), an expert in the field of DD, trained the examiner in hand examination and recognizing (early) signs of DD and other causes of palmar lumps and finger contractures. The first 30 participants were examined independently by both the examiner (BB) and the senior author (DB). Any inconsistencies were discussed.

All participants were examined at their home, with the exception of some participants who refused a home visit; they were instead examined at the outpatient clinic of our hospital (n = 10). The examination entailed close inspection and palpation of the palm, dorsum and fingers of both hands for signs of DD, and knuckle pads.

Information about potential predictors was gathered by using a paper version of a self-reported survey. Of the participants of the prevalence study in 2012 who had been diagnosed with DD, 57 (14%) individuals were included in a longitudinal study about the natural course of DD.[7] Because these patients had already been examined for DD progression by a senior author (DB) in 2019, the data of those assessments were used in the current study. These participants provided a written informed consent for reuse of their data.

Statistical analysis. The characteristics of the participants were presented by means and standard deviations (SDs) for normally distributed, continuous variables. Non-normally distributed continuous variables and ordinal variables were described by medians with interquartile ranges (IQRs).

For dichotomous variables, frequencies and proportions were reported. Differences in clinical characteristics between the subgroups were determined by univariate regression analyses.

The proportion of participants having disease progression was calculated by dividing the number of participants that had progression or surgical treatment in one or multiple fingers, by the number of participants diagnosed with DD at study entry in 2012 (population at risk for progression). For each disease stage at study entry (Iselin stage I to IV) the rate of disease progression was compared using Fisher's exact test. The proportion of participants with formation of new DD was calculated by dividing the number of participants who have formed DD by the number of participants who were not diagnosed with DD in 2012. The covariates that are potential predictors for the progression of DD and new formation of DD were determined by multivariable logistic regression analyses.

Because we were interested in the predictive effect of the covariates on disease progression and DD development, we used the values of the covariates that were assessed in 2012 in our models. The predictor "alcohol consumption" was categorized as 'none', 'non-excessive' or 'excessive', which was defined according to the Netherlands Institute of Mental health and addiction.[12] Since the logit-plot showed no linear relationship between age and the outcome variable, age was dichotomized into two groups of comparable size: age < 60 years or ≥ 60 years. The presence of Ledderhose's disease and knuckle pads, were added together as the covariate "ectopic lesions". "Hypertension" and "hypercholesterolaemia" were categorized as 'yes', 'never/unknown', and 'no, not anymore'. If a participant was a smoker in 2012 but had discontinued smoking by 2019, or reported to have smoked for > one year in the past, this was classified as 'quit'. Epilepsy was not included in the regression analysis, because only two participants were affected. Covariates with a p-value < 0.20 in the univariate regression analyses were included in the multivariable regression models. Using backward elimination, the final model was determined. A two-sided p-value < 0.05 was considered as significant. All statistical analyses were performed by using SPSS Statistics for Windows, Version 23.0 (IBM, USA).

Results

Of the fixed cohort of 763 individuals, 398 (52.2%) participated in the study (Figure 1).

Course and progression of DD. First, we calculated the proportion of participants who developed DD or had disease progression. Of the 398 participants, 143 (35.9%) were diagnosed with DD at follow-up examination, of whom 56 (39.2%) were newly diagnosed and had developed DD in the seven years since the first population study (Table II). Out of 143 participants with contemporary manifestation of DD, 93 were already diagnosed with DD in 2012 (Table III). Six out of 93 participants (6.5%) diagnosed with DD in 2012 showed no signs of DD in 2019, and 67 out of 93 participants (72.0%) showed stable disease since the original study. In total, 20 (21.5%) out of 93 participants affected by DD in 2012, showed disease progression.

Table III. Characteristics of participants at risk of progression and results of univariate logistic regression analyses.

Participants (n = 93)	No progression after seven years	Progression after seven years	Odds ratio (95% CI)	p-value*
Participants, n (%)	73 (78.5)	20 (21.5)		
Male, n (%)	38 (52.0)	15 (75.0)	2.73 (0.91 to 8.40)	0.073
Age, n (%)				
< 60 yrs (reference)	15 (20.5)	3 (15.0)		
≥ 60 yrs	58 (79.5)	17 (85.0)	0.68 (0.18 to 2.64)	0.580
Median age at inclusion (2012), yrs (IQR)	68 (61 to 74)	65 (61 to 73)		
Diabetes n (%)	11 (15.1)	1 (5.0)	0.30 (0.04 to 2.45)	0.259
Hypercholesterolaemia n (%)				0.293†
Never/unknown (reference)	41 (56.2)	13 (65.0)		
No, not anymore	21 (28.8)	2 (15.0)	0.30 (0.06 to 1.46)	0.135
Yes	5 (2.7)	3 (10.0)	1.26 (0.22 to 7.29)	0.795
Missing	6 (8.2)	3 (15.0)		
Hypertension, n (%)				0.780†
Never/unknown (reference)	41 (56.2)	13 (65.0)		
No, not anymore	25 (34.2)	6 (30.0)	0.76 (0.26 to 2.25)	0.616
Yes	6 (8.2)	1 (5.0)	0.53 (0.06 to 4.78)	0.526
Missing	1 (1.4)	0 (0.0)		
Smoking, n (%)				0.568†
No (reference)	28 (38.4)	6 (30.0)		
Yes	10 (13.7)	2 (10.0)	0.93 (0.16 to 5.40)	0.939
Quit	33 (45.2)	12 (60.0)	1.70 (0.56 to 5.11)	0.347
Missing	2 (2.7)	0 (0.0)		
Alcohol intake (units per week), n (%)				0.614†
None (reference)	20 (27.4)	4 (20.0)		
≤ 14 females or ≤ 21 males	44 (60.3)	12 (60.0)	1.36 (0.39 to 4.76)	0.626
> 14 females or > 21 males	9 (12.3)	4 (20.0)	2.22 (0.45 to 10.94)	0.326
First-degree relative with Dupuytren's disease, n (%)	13 (17.8)	9 (45.0)	3.77 (1.30 to 10.96)	0.015
Manual labour n (%)	22 (31.5)	7 (35.0)	1.17 (0.41 to 3.32)	0.767
Hand injury, n (%)	24 (32.9)	3 (15.0)	0.36 (0.10 to 1.35)	0.130
Dexterity, n (%)				0.755†
Left (reference)	4 (5.5)	2 (10.0)		
Right	66 (90.4)	17 (85.0)	0.52 (0.09 to 3.05)	0.465
Bimanual	3 (4.1)	1 (5.0)	0.68 (0.04 to 11.29)	0.779
Ectopic lesions, n (%)‡	16 (21.9)	9 (45.0)	2.81 (0.99 to 7.97)	0.052
Missing	2 (2.7)	0 (0.0)		

*Univariate logistic regression.
†Significance value for the overall effect of the covariate.
‡Ledderhose's disease or knuckle pads present.
CI, confidence interval; IQR, interquartile range.

Table IV. Results of the multivariable logistic regression model for progression of Dupuytren's disease.

Risk factor	Odds ratio (95% CI)	p-value*
First degree relative	4.99 (1.51 to 16.49)	0.008
Ectopic lesions	3.23 (1.027 to 10.14)	0.045

*Multivariable logistic regression.
CI, confidence interval.

We then compared the disease progression rates of patients with early disease (stage I) at study entry and patients with advanced disease (stage II or III) at study entry. Out of 82 participants with early DD who were included in the 2012 study, 13 (15.9%) had developed a joint contracture (n = 11, 13.4%) or had undergone surgery (n = 2, 2.4%) seven years later. Four out of five participants (80%) with stage II at study entry had progressed to stage III (n = 3, 60%) or had surgery (n = 1, 20%). The three participants who initially had stage III all had surgery (Table II). The progression rates between the different initial disease stages differ significantly ($p < 0.001$, Fisher's exact test).

At follow-up examination, 115 out of 143 (80.4%) participants affected by DD only had palmar nodules or cords (Iselin stage I), and the remaining 28 (19.6%) participants had finger contractures in one or more rays (Iselin Stage II and III) or had surgery. There were no patients with Iselin stage IV. Out of 488 affected rays, the ring finger was most frequently affected (n = 176, 36.1%), followed by the little finger (n = 119, 24.4%), middle finger (n = 110, 22.5%), thumb (n = 62, 12.7%), and index finger (n = 21, 4.3%) (Supplementary Table ii). Disease progression was mostly present in the ring finger (14 out of 27 rays, 51.9%) (Supplementary Table iii).

Predictors of progression. We compared clinical characteristics between individuals with disease progression and individuals without disease progression (Table III). Univariate logistic

Table V. Characteristics of participants newly diagnosed with Dupuytren's disease.

Participants (n = 305)	No Dupuytren's disease	New Dupuytren's disease	Odds ratio (95% CI)	p-value*
Participants, n (%)	249	56		
Male, n (%)	107 (43.0)	28 (50.0)	1.33 (0.74 to 2.37	0.340
Age, n (%)				
< 60 yrs (reference)	143 (57.4)	29 (51.8)		
≥ 60 yrs	106 (42.6)	27 (48.2)	1.26 (0.70 to 2.25)	0.442
Median age at inclusion (2012), yrs (IQR)	58 (54 to 64)	59 (56 to 66)		
Diabetes, n (%)	18 (7.2)	8 (14.3)	2.14 (0.88 to 5.20)	0.094
Hypercholesterolaemia, n (%)				0.156†
Never/unknown (reference)	29 (51.8)	159 (63.9)		
No/not anymore	19 (33.9)	71 (28.5)	1.47 (0.77 to 2.79)	0.242
Yes	8 (14.3)	19 (7.6)	2.31 (0.92 to 5.77)	0.073
Hypertension, n (%)				0.193†
Never/unknown (reference)	31 (55.4)	144 (57.4)		
No, not anymore	18 (32.1)	92 (36.9)	0.90 (0.48 to 1.71)	0.752
Yes	7 (12.5)	14 (5.6)	2.31 (0.86 to 6.19)	0.097
Smoking, n (%)				0.093†
No (reference)	98 (39.4)	16 (28.6)		
Yes	65 (25.7)	12 (21.4)	1.15 (0.51 to 2.59)	0.738
Quit	85 (34.1)	28 (50.0)	2.02 (1.02 to 3.98)	0.043
Missing	2 (0.8)	0 (0.0)		
Alcohol intake (units per week), n (%)				0.777†
None (reference)	73 (29.3)	14 (25.0)		
≤ 14 females or ≤ 21 males	161 (64.7)	39 (69.6)	1.26 (0.65 to 2.47)	0.495
> 14 females or > 21 males	15 (6.0)	3 (5.6)	1.04 (0.27 to 4.08)	0.952
First-degree relative with Dupuytren's disease, n (%)	18 (7.2)	3 (5.4)	0.72 (0.21 to 2.55)	0.614
Missing	1 (0.4)	0 (0.0)		
Manual labour, n (%)	90 (36.1)	18 (32.1)	0.84 (0.45 to 1.55)	0.572
Hand injury, n (%)	58 (23.3)	21 (37.5)	1.98 (1.06 to 3.66)	0.030
Dexterity, n (%)				0.626†
Left (reference)	34 (13.7)	5 (8.9)		
Right	213 (85.5)	51 (91.1)	1.63 (0.61 to 4.37)	0.333
Bimanual	2 (0.8)	0 (0.0)		0.999
Ectopic lesions, n (%)‡	41 (16.5)	5 (8.9)	0.50 (0.19 to 1.32)	0.161

*Univariate logistic regression.
†Significance value for the overall effect of the covariate.
‡Ledderhose's disease or knuckle pads present.
CI, confidence interval; IQR, interquartile range.

regression analyses showed that male sex, having a first-degree relative affected by DD, previous hand injury and ectopic lesions were potential predictors for progression of DD ($p < 0.20$). Multivariable analysis showed that having a first-degree relative and having ectopic lesions are both significant predictors for the progression of DD (Table IV).

Predictors of new formation of DD. Out of 305 previously unaffected participants, 56 (18.4%) have developed DD during the previous seven years. Univariate logistic regression analyses revealed that diabetes, hypercholesterolaemia, hypertension, smoking, previous hand injury and ectopic lesions were potential predictors for new formation of DD ($p < 0.20$) (Table V). Multivariable analyses revealed that previous hand injury is a significant predictor for new formation of DD (odds ratio (OR) 2.01, 95% CI 1.07 to 3.75; $p = 0.029$).

Discussion

Our study reveals that 20 out of 93 (21.5%) participants with subclinical DD show disease progression after seven years of follow-up. The higher the initial disease stage at inclusion, the greater the proportion of participants who had disease progression at follow-up. Patients having an affected first-degree family member and those with ectopic lesions are at higher risk of disease progression. From the 305 participants previously being unaffected, 56 (18.4%) have developed DD. Individuals who had sustained a previous hand injury are at higher risk of developing DD.

A previous study described a progression rate of 51% from palmar nodules to cords after an mean follow-up time of 8.7 years.[8] However, that study was a retrospective analysis of patient files. It reflected the clinical population included, showing it is likely that patients from a hospital population are more susceptible to progression than a subclinical population. One study among a general population showed that 37.9% of the participants had disease progression to joint contractures or surgery within the follow-up period of 18 years.[9] If we applied the same definition for progression and corrected for the difference in duration of follow-up by extrapolation, we estimate that we would have found a progression rate of 41.8% after 18 years.

It is noteworthy that the progression rate we reported is the maximal progression rate in our population, due to our method of classification of participants. When a participant had progressive disease in one ray but showed stable disease or was downgraded in another ray, one was still classified as having progression.

The factors that we found to be predictive for progression (affected family members and ectopic lesions), are part of the Dupuytren's diathesis, which relates to features that are thought to predispose to an aggressive disease course.[13] It is, however, important to note that all previous studies were conducted among a clinical population, in contrast to our study. Our findings show that these specific Dupuytren's diathesis factors are also relevant in estimating risk of progression in a subclinical Dupuytren's population.

We report that 56 (18.4%) out of 305 participants being unaffected with DD in 2012 have developed DD seven years later. If we consider our findings in terms of new disease cases per year, we find an incidence rate of 2.9 per 100 person years, which is in line with previous reported incidence rates in a general population.[9] A much lower incidence rate of 0.34 per 100 person years (0.03%) has also been reported.[14] However, subclinical Dupuytren patients were not included, since this previous study was performed using data from general practitioners.

Several studies, including a cross-sectional study and several case reports, suggest that hand injury triggers the development of DD.[15,16] This is in accordance with our finding that previous hand injury is predictive for the formation of new DD. However, the degree of injury, the side of the injury and the interval between injury and developing DD were not assessed. Therefore, the causal relationship between hand injury and formation of new DD needs further elucidation.

In our study, six participants (6.5%) were downgraded; they had one or multiple palmar nodules in 2012, while in 2019, no signs of DD were recognized. A possible explanation is the occurrence of spontaneous regression, which has been reported in the literature.[8,17] This is of relevance for any treatment of early disease where regression may be attributed to the treatment, but in fact it is the natural course. Downgrading might also be caused by interobserver variation. Although the criteria for diagnosing DD did not differ between both measurements, early palmar nodules are sometimes hard to diagnose, which raises the chance of misclassification bias.[18] Another theory is the distinction between DD and non-DD, a fascial proliferation with a non-progressive or sometimes regressive course in which environmental factors such as trauma play a role in the pathogenesis.[19] It might be that some of the participants with downgrading had traumatic palmar fibrosis, resolving in the course of time.

One of the strengths of this study is that it is an extension of a study in which a random sample of the general population was included. Therefore, we examined a largely subclinical population which is important for reliably predicting progression of primary, untreated DD. Out of 763 subjects involved in 2012, 674 were potentially available for inclusion in the current study. Among them, 102 subjects (15.1%) were not willing to participate. This potentially introduced selection bias (e.g. subjects with symptoms more frequently participated than subjects having without any symptoms).We however limited the chance of selection bias by visiting the participants at home instead of inviting them to the hospital. A third strength of our study was the method of data collection. The examiner (DB) that examined the participants in the natural course study (n = 57), trained the examiner that assessed the remaining participants (BB) (n = 341) in diagnosing DD at an early and advanced stage. Therefore, we limited the intra-observer variability as much as feasible.

This study has some limitations. First, the examiner was not the same as in 2012, and was blinded for the previous observations. This could have resulted in misclassification bias. However, without being influenced by previous observations, the examiner could classify all participants objectively and consistently, eliminating confirmation bias.

Second, we decided to report our findings on a participant level, and not on a finger level. This causes a simplification of reality, as different fingers in the same participant can have different disease courses. Since we reported the highest possible rate of progression in our cohort, it might have led to an overestimation of the true progression rate. The progression rate calculated at a finger level would probably be lower. However, it is clinically relevant whether an individual has progression. To know in which fingers the progression occurs, is less important. Furthermore, predictors are often factors that occur on a participant level (e.g. the person is male/female, and sex does not differ between fingers). Presenting predictors on a finger level has no clinical meaning and complicates the analyses and interpretation.

A substantial part of our initial study population was lost to follow-up. Hypothetically, this could be explained by the lack of benefit to participate, the long interval between measurements and increased age of the study population. Because our population includes individuals from a specific region in the Netherlands in which demographics may differ from other national and international regions, our findings may not be generalizable.

As we did not assess for ethnicity and age of onset, this study does not cover all factors that are known to be part of the Dupuytren's diathesis. However, within the greater area of the city of Groningen, there is no large ethnic diversity.[20] Therefore, we expect that it would be hard to identify significant signals with regard to ethnicity as a predictor for progression of DD.

Several factors are assessed retrospectively, such as hypercholesterolaemia and hand injury, and all factors were self-reported. Moreover, the side of the hand being injured was not specified, which potentially causes an underestimation of its true effect.

Lastly, we did not measure changes in the angle of contracture, which is the common denominator in the assessment of DD treatment results.[21] However, the use of goniometric data might have led to a high misclassification rate of disease progression due to the limited accuracy when measuring angles in DD by goniometry.[22] For the purpose of this study, we consider the use of the Iselin classification to be a suitable and efficient method to assess disease progression in a subclinical DD population.

In conclusion, this study shows that progression of DD occurs in 21.5% of the subclinical population over a period of seven years. The higher the initial disease stage, the greater the proportion of participants who had disease progression seven years later. We found that having affected family members and ectopic lesions are predictive for disease progression. These predictors are known to be part of the Dupuytren's diathesis and appear to be not only applicable to the clinical population, but also to the subclinical population. This study is a first initiative in the development of a prediction model of progression of DD, which is required for the application of potentially preventive therapies in the future.

Take home message

- Over a period of seven years, progression of Dupuytren's disease (DD) only occurs in one out of five affected individuals in a general population.
- The higher the initial disease stage, the greater the proportion of participants who have disease progression seven years later.
- This study is a first initiative in the development of a prediction model of progression of DD, which is required for the application of potentially preventive therapies in the future.

Supplementary material

Decision tree of patient classification, and tables showing characteristics of the complete cohort, total number of rays affected by DD, and total number of rays with progression of DD.

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