# Disease course of primary Dupuytren's disease

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**Disease course of primary Dupuytren's disease: 5-year results of a prospective cohort study**

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**Short running head:** Course of primary Dupuytren's disease

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**ABSTRACT**

BACKGROUND: Predicting progression of Dupuytren's disease (DD) becomes relevant in an upcoming era with progression-preventing treatment. This study aimed to 1) determine the disease course of DD, and 2) identify factors associated with progression.

METHODS: 258 DD patients participated in this prospective cohort study, obtaining 17,645 observations in 5 years. Outcomes were disease extent (surface area) and contracture severity (total passive extension deficit, TPED). Demography, lifestyle, health status, exposure to manual work and genetic risk scores were gathered as potential predictors. Subject-specific mixed-effects models were used to estimate disease course, and logistic regression with LASSO was used to evaluate factors associated with the presence of progression.

RESULTS: On average, DD was progressive in all finger rays with regard to area (yearly increase 0.07[95% CI: 0.02-0.13] - 0.25[95% CI: 0.11-0.39] $cm^2$). Progression in TPED was only present on the small finger side (yearly increase 1.75[95%CI: 0.30-3.20] - 6.25[95%CI: 2.81-9.69]$^o$). Stability or regression in area and TPED was observed in respectively 11 and 13%, and 16 and 15% (dominant and non-dominant hands). Smoking, cancer, genetic risk score and hand injury were univariate associated with progression in area, but after multivariate variable selection none of these associations remained. No predictors for progression in TPED were found.

CONCLUSIONS: DD is progressive, especially with respect to disease extent. Progression in contracture severity is mainly present on the small finger side of the hand. None of the traditional risk and diathesis factors were associated with progression, indicating that we might need new hypotheses about DD progression.

## INTRODUCTION

Dupuytren's disease (DD), with its prevalence ranging between 1-32% in the general population,[1] is the most common organ-specific fibrosis.[2] It has been associated with chronic diseases such as diabetes mellitus,[3] but also with an increased risk of mortality due to a several diseases including cancer, cardiovascular and respiratory disease.[4-7]

From a clinical point of view, it is often thought that DD is progressive. This is underlined by findings of lab studies indicating that disease extension and contracture formation is a self-propagating process.[8-10] However, the few studies evaluating natural course of DD consistently show that the minority of the patients has progression.[11-14] The interpretation of these findings is hampered by the fact that progression is only presented as the percentage of hands progressing to a next disease stage.[11, 12] Furthermore, previous studies often have only two measurements, making it impossible to determine the exact disease course profile.[13, 14] Most importantly, none of the previous studies was aimed to identify predictors for a progressive disease course.

Precise knowledge about the disease course is important to gain insight in the development of the disease, to provide patients with evidence-based information during counseling, and to facilitate the timing of treatment. Additionally, finding factors that predict progression helps to identify the subpopulation at highest risk of progression. This has become increasingly relevant, since recent scientific breakthroughs resulted in the development of a potential treatment for preventing DD progression.[10, 15] However, this treatment is costly and not fully without risks,[16, 17] which demonstrates the urgency of being able to identify the target population who will benefit from future treatment aimed at

preventing progression, and thereby limiting patient- and economic burden related to unnecessary treatment in those with non-progressive disease.

The current study was conducted to answer the following research questions: 1) What is the average and individual long-term natural course of DD, and 2) What factors are associated with progression?

## METHODS

### *Design*

In this prospective cohort study, measurements took place with an interval of 6 months. Data gathered between May 2012 and August 2017 were included in the current analysis.

### *Participants*

A total of 462 adult patients, who had primary (i.e. untreated) DD in one or both hands, were asked to participate. Untreated hands of patients who were unilaterally treated were also eligible for inclusion. Participants were recruited from two sources: 1) from a random age-stratified sample of the general elderly population of the city of Groningen (The Netherlands) who had been included in a previous study of our research group (n = 179, subclinical population)[18], and 2) from DD patients who visited the outpatient clinic of the department of Plastic Surgery for a consult on DD (n = 283, clinical population). A sample size calculation was not performed, since no data is available from comparable studies on long-term disease course. We estimated that after 5 years, data of 200 participants would be sufficient for statistical analyses. Taking drop-out into account, we aimed to include at least 250 participants.

This study was reviewed and approved by the institutional ethics committee (METc2011/397), conducted in accordance with the 1964 Declaration of Helsinki and all participants gave written informed consent.

***Outcome measures***

The primary outcome measures were disease extent and severity of contracture. Disease extent was determined by physical examination of the hands, in which the nodules and cords were marked on the skin with a skin pencil. We used the surface area of nodules and cords measured with a tumorimeter to quantify disease extent,[19] which was summed per ray to obtain total area per ray. Contracture severity was determined by measuring the passive extension deficit (i.e. the inability to passively straighten the finger) of each finger joint, using a goniometer. These extension deficits were summed to obtain total passive extension deficit (TPED) per finger. TPED was not measured in the thumb, as DD cords in the thumb rarely lead to functional restraints. Contractures of cords in the first web space can lead to functional problems, but this is not captured by measuring TPED.

***Predictor variables***

Predictor variables of progression were sex, age, age of onset, familial occurrence of DD, (past) exposure to vibration or heavy manual work during occupational or leisure activities, smoking and drinking habits, (past) hand injuries, abnormal scar formation, diabetes mellitus, liver disease, epilepsy, cancer, Ledderhose's disease (fibromatosis on the soles of the feet), Peyronie's disease (fibromatosis in the penis), knuckle pads (fibrous masses on the dorsal side of the first finger joints) and weighted genetic risk score. These variables were obtained by an anamnestic interview during all follow-up measurements. In case of doubt about the presence of Ledderhose's disease based on anamnesis, the feet were examined. The presence of knuckle pads was also determined by physical examination. A weighted

genetic risk score was calculated from DNA derived from blood samples, based on the 26 SNPs currently known to be associated with DD,[20] using PLINK software.

***Procedures***

Data of the first 1.5 years were gathered by the second author, while the first author gathered data during subsequent visits. An inter-observer agreement study was done to evaluate the necessity of adjustment for observer.[19] All measurements were done using the exact same instruments.

Every 6 months, the participants visited the outpatient clinic of the department of Plastic Surgery for this study. In case the participant was not able to visit the hospital, e.g. due to injuries, the examiner visited the participant at home if possible. Some participants refused to visit the hospital every 6 months, and they were asked to continue participation with a yearly visit to prevent drop-out.

***Statistical Analysis***

Characteristics of the cohort were described using descriptive statistics (frequencies, percentages, means, standard deviations, medians and interquartile ranges) for predictors and outcome measures.

Missing values in the outcomes were scarce (89/17 645 observations), and most predictor variables had no missing values at all. However, self-reported age of onset, weighted genetic risk score, heavy manual work, and hobbies with heavy manual work, all showed high

proportions of missing values. We decided not to use multiple imputation, as these variables are not likely to be missing at random. These variables were excluded casewise.

Gathered data from dropped-out participants was included in the current analyses, as well as preoperative data from participants who received treatment during the course of the study. The statistical analysis was applied to the surface area of nodules and cords, and to the TPED separately. These outcomes were summed per ray.

To answer the first research question, we fitted individual, linear trajectories using a subject-specific mixed-effect model, as no evidence for non-linearity was observed. Follow-up time was defined per finger ray and outcome separately, starting from the first time at which a clinical symptom was present (area or TPED > 0). For the linear trajectories, the logarithm of the intercept (area/TPED at baseline) and slope (progression) was considered bivariate normally distributed. We took the intercept lognormal to guarantee a positive area/TPED at the first time point at which a clinical symptom was observed. The model was fitted using procedure NLMIXED of SAS Institute, version 9.4. The parameter estimates for intercept and slope, the correlation between intercept and slope, and the relative standard deviations are reported. The observations were predicted by the random effects derived from the subject-specific model, using best linear unbiased prediction. This was done to enable the calculation of $R^2$ values to evaluate how much variability between outcome and predictions is explained by the model, estimated with procedure GLM of SAS Institute, version 9.4.

To answer the second research question, the observed area and TPED were aggregated into observations in the dominant and non-dominant hand. We analysed the association of the baseline covariates with predicted progression (slope being positive or not) obtained

from the analysis described above. The baseline covariates included in the model were sex, age, age of onset, smoking (never/ever), alcohol (never/ever), manual work during occupational and leisure activities, vibration, hand injury, Peyronie's disease, Ledderhose's disease, knuckle pads, abnormal scarring, diabetes, epilepsy, liver disease, cancer, having a first degree relative with DD, and genetic risk score. The latter was included as continuous variable in the model, the other variables as dichotomous. We assessed the effect of each covariate on progression separately, but variable selection was done using logistic regression with LASSO and the Bayesian Information Criterion on the variables that had a p-value < 0.05 at the variable screening stage. This analysis was done with procedure HPGENSELECT of SAS Institute, version 9.4.

**RESULTS**

Of 462 eligible patients, 258 patients with untreated DD in at least one hand decided to participate; 111 subclinical patients recruited from the general population, and 147 from the clinical population. A total of 8 and 86 participants of the subclinical and clinical population respectively, were already treated in one hand at start of the study, so only their untreated hand was included in this study. Women and patients from the general population were more frequently willing to participate, compared with men and patients from the clinical population (Supplementary Material 1). A total of 77 dropped-out during the study due to various reasons (Figure 1), leaving 181 active participants after 5 years (Table 1).

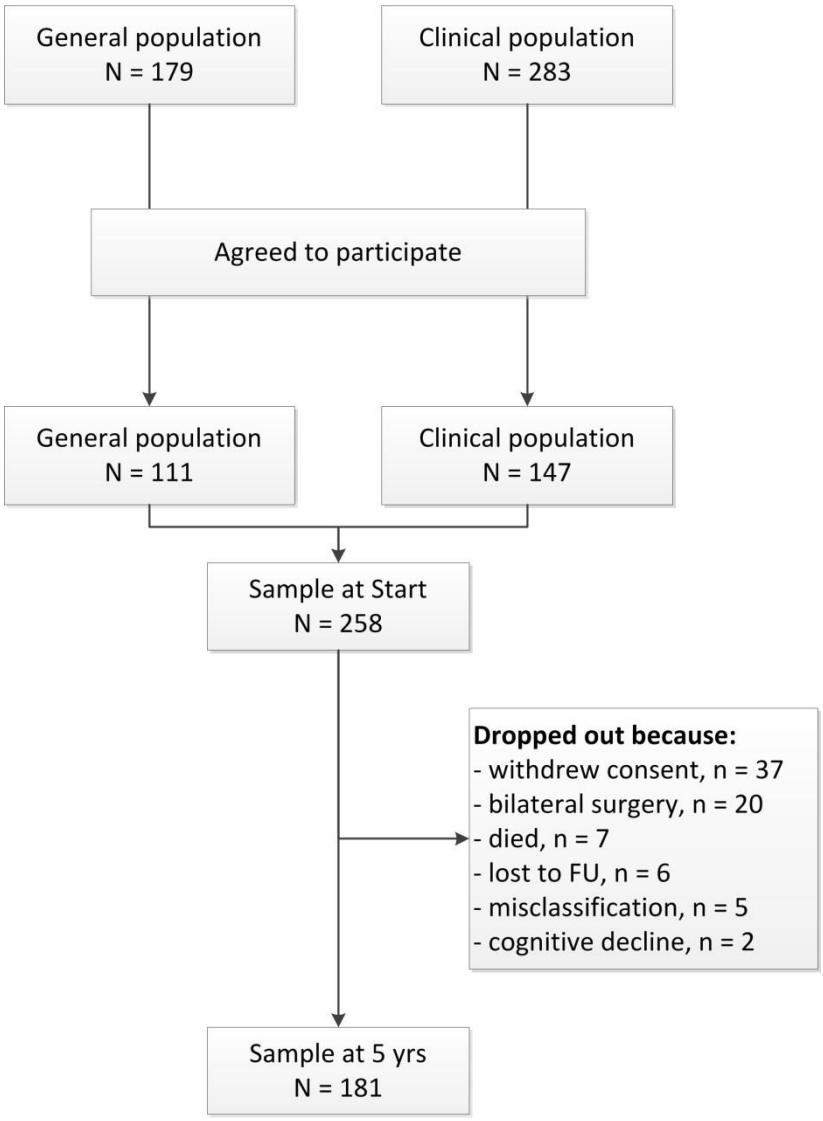


Figure 1. Flow-chart of the study, indicating the number of participants across time and reasons for drop-out.

Table 1. The number of participants and subjects with available data presented for each measurement time. The number of participants and cases with available data during each measurement time are not equal, since some participants were not able to attend each measurement time. The number of participants with available data is lower at T7-T10, as not all participants were included at the same time.

| | **T0** | **T1** | **T2** | **T3** | **T4** | **T5** | **T6** | **T7** | **T8** | **T9** | **T10** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Follow-up (yrs) | Start | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 4.5 | 5.0 |
| Participants (n) | 258 | 252 | 245 | 231 | 218 | 206 | 201 | 196 | 188 | 185 | 181 |
| Available data (n) | 258 | 245 | 238 | 224 | 204 | 189 | 191 | 173 | 171 | 169 | 163 |

Yrs: years, N: number of Subjects

The sample consisted of 163 men and 95 women, with a mean age of 64.7 ± 10.3 at inclusion (Table 2). The majority of the participants were smokers or former smokers, and for those, a median of 16.3 (IQR: 5.0 – 27.2) pack years was found. Among the participants who consumed alcohol, a median of 7 (IQR: 2.8 – 13.5) glasses per week was reported. The median time of follow-up was 4.9 (IQR: 2.4 – 5.0) years, and in this period, 2215 patient exams were performed.

Table 2. Characteristics of the cohort.

| | N (%) | N missing (%) |
|---|---|---|
| **Demographics** | | |
| *Male gender* | 163 (63.2) | 0 (0.0) |
| *Age at inclusion, mean (SD)* | 64.7 (10.3) | 0 (0.0) |
| *Self-reported age of onset, mean (SD)* | 54.4 (11.9) | 59 (27.2) |
| *wGRS, mean (SD)*[a] | 6.134 (0.837) | 34 (13.2) |
| *Hand dominance* | | 1 (0.4) |
| Left | 21 (8.1) | |
| Right | 233 (90.3) | |
| Bimanual | 3 (1.2) | |
| **Intrinsic risk factors** | | |
| *First degree relative with DD* | 108 (41.9) | 1 (0.4) |
| *Diabetes* | 29 (11.2) | 0 (0.0) |
| *Liver disease* | 5 (1.9) | 0 (0.0) |
| *Epilepsy* | 3 (1.2) | 0 (0.0) |
| *Scarring* | | 1 (0.4) |
| Normal | 250 (96.9) | |
| Hypertrophic | 3 (1.2) | |
| Keloid | 4 (1.6) | |
| *Ledderhose's disease* | 27 (10.5) | 0 (0.0) |
| *Peyronie's disease (only in men)* | 13 (8.0) | 0 (0.0) |
| *Knuckle pads* | 86 (33.3) | 0 (0.0) |
| *Cancer* | 5 (1.9) | 0 (0.0) |
| **Extrinsic risk factors** | | |
| *Heavy manual work* | 102 (39.5) | 34 (15.7) |
| *Hobbies with heavy manual work* | 112 (43.4) | 42 (16.3) |
| *Exposure to vibration* | 173 (67.1) | 6 (2.3) |
| *Hand injury* | 108 (49.8) | 5 (2.3) |
| *Smoking status* | | 0 (0.0) |
| Current | 38 (14.7) | |
| Former | 152 (58.9) | |
| Never | 68 (26.4) | |
| *Alcohol consumption* | | 0 (0.0) |
| Current | 215 (83.3) | |
| Former | 11 (4.3) | |
| Never | 32 (12.4) | |

N: number, wGRS: weighted genetic risk score, DD: Dupuytren's disease

[a] Natural logarithm of wGRS

***Natural course of Dupuytren's disease – Area of nodules and cords***

On average the area of nodules and cords increased over time, in all finger rays of both hands (Table 3). As example, the area of nodules and cords in the right thumb ray increased yearly with 0.23 $cm^2$ on average. This appears to be only a small increase, but this concerns an increase per year. Over the course of 5 years, surface area in the right thumb ray would increase on average with 1.15 $cm^2$, which is equivalent to the formation of a new cord with a length of 2.3 cm and width of 0.50 cm. The relatively wide confidence intervals (especially for the right index, and left thumb, index, and small finger) indicate that variability between participants was substantial. The disease extent at start of the study was not correlated to progression (Table 3, correlation), except for the right index finger ray. We observed no large differences in increase in area between the left and right hand, nor between left and right finger rays. In both hands, the ring finger ray was most frequently affected, followed by the small and middle finger ray. When the surface area of all fingers is summed per hand, we observed a yearly increase of 0.51 (95%CI: 0.41-0.61) $cm^2$ in the dominant and 0.60 (95%CI: 0.49-0.72) $cm^2$ in the non-dominant hand. The standard deviations in yearly increase between participants, were 0.59 (95%CI: 0.52-0.67) $cm^2$ in the dominant and 0.75 (95%CI: 0.66-0.85) $cm^2$ in the non-dominant hand, indicating substantial heterogeneity in progression. This is further underlined by the finding that 11.4 and 12.9% of the participants did not show an increase or even showed a decrease in area in the dominant and non-dominant hand, respectively.

Table 3. Parameter estimates [95% confidence intervals] and model fit of the subject-specific model examining the surface area at start of the study (A), increase in area over time (B), and the correlation between these two aspects.

| AREA | | N fingers | A) Disease extent at start ($cm^2$) | B) Yearly increase ($cm^2$) | Correlation A – B | $R^2$ |
|---|---|---|---|---|---|---|
| Right | Thumb | 85 | 0.91 [0.77; 1.08] | 0.23 [0.15; 0.31] | 0.18 [-0.19; 0.55] | 84.8 |
| | Index | 48 | 0.52 [0.35; 0.78] | 0.13 [0.02; 0.24] | -0.52 [-0.91; -0.13] | 86.0 |
| | Middle | 121 | 0.90 [0.80; 1.02] | 0.07 [0.02; 0.13] | 0.13 [-0.09; 0.35] | 90.5 |
| | Ring | 163 | 1.44 [1.29; 1.60] | 0.13 [0.08; 0.17] | 0.10 [-0.09; 0.30] | 90.5 |
| | Small | 130 | 0.95 [0.81; 1.12] | 0.17 [0.11; 0.23] | 0.08 [-0.15; 0.31] | 90.4 |
| Left | Thumb | 98 | 0.86 [0.74; 1.00] | 0.20 [0.13; 0.28] | -0.10 [-0.40; 0.19] | 87.0 |
| | Index | 40 | 0.56 [0.35; 0.91] | 0.25 [0.11; 0.39] | 0.38 [-0.04; 0.80] | 94.2 |
| | Middle | 134 | 0.90 [0.77; 1.04] | 0.07 [0.02; 0.13] | -0.15 [-0.39; 0.09] | 89.2 |
| | Ring | 168 | 1.31 [1.15; 1.50] | 0.17 [0.12; 0.22] | 0.12 [-0.09; 0.33] | 92.6 |
| | Small | 138 | 0.97 [0.79; 1.17] | 0.19 [0.09; 0.28] | -0.13 [-0.35; 0.08] | 93.7 |

$R^2$: model fit.

### *Natural course of Dupuytren's disease – TPED*

We found that on average, TPED increased over time in the right ring finger, and the left ring and small finger (Table 4). In the other fingers, TPED was stable. TPED in the index finger could not be estimated because of the small number of participants with index finger contractures. A minority (n = 126) of the participants had or developed finger contractures during the course of the study, and among those, TPED at start of the study was relatively small. There was no correlation between the TPED at start of the study and the yearly increase. Contractures were most frequently present in the ring and small fingers, and half

as frequently in the middle fingers. The standard deviations in yearly increase between participants, ranged between 0.51° (95%CI: 0.19-1.36) for the left small finger, and 10.10° (95%CI: 7.53-13.5) for the left ring finger, again indicating substantial heterogeneity. This is further underlined by the finding that 15.7 and 14.8% of the participants did not show a TPED increase or even showed decrease in the dominant and non-dominant hand, respectively.

Table 4. Parameter estimates [95% confidence intervals] and model fit of the subject-specific model examining the TPED at start of the study (A), increase in TPED over time (B), and the correlation between these two aspects.

| TPED | | N fingers | A) TPED at start (°) | B) Yearly increase (°) | Correlation A – B | $R^2$ |
|---|---|---|---|---|---|---|
| Right | Middle | 32 | 9.97 [6.45; 12.5] | 1.25 [-0.65;3.15] | -0.11 [-0.80; 0.58] | 84.0 |
| | Ring | 65 | 7.03 [5.01; 9.88] | 4.59 [2.74; 6.45] | 0.05 [-0.31; 0.42] | 92.0 |
| | Small | 57 | 10.1 [6.49; 15.6] | 2.12 [-0.02;4.26] | 1.00 [NA;NA] | 89.1 |
| Left | Middle | 32 | 10.6 [7.34; 15.4] | -0.21 [-3.09;2.67] | 0.73 [0.34; 1.00] | 90.7 |
| | Ring | 60 | 7.19 [4.74; 10.9] | 6.25 [2.81; 9.69] | 0.38 [-0.09;0.84] | 85.8 |
| | Small | 57 | 15.7 [11.2; 22.2] | 1.75 [0.30; 3.20] | 0.27 [-0.26; 0.81] | 91.1 |

TPED: total passive extension deficit; $R^2$: model fit.

***Factors associated with progression***

In the univariate analyses on predictors of progression in disease extent (area), we found that smoking ($p = 0.010$), cancer ($p = 0.045$) and the weighted genetic risk score ($p = 0.024$) were associated with progression in the dominant hand. In the non-dominant hand, ipsilateral hand injury ($p < 0.001$) was associated with progression. For TPED, in both hands

no associations were identified. After applying variable selection (multivariate analysis), no covariates were found to contribute to progression of area or TPED in either hands. This indicates that the associations found are no strong predictors of progression.

## DISCUSSION

### *Primary findings*

This study demonstrated that DD is progressive, especially with respect to disease extent (area). Progression in contracture severity (TPED) is mainly present on the small finger side of hand. There was substantial heterogeneity among participants, with some having severe progression and also some who had stable or regressive disease in both area and TPED. Surprisingly, we found no variables that predicted presence of progression after applying variable selection methods.

### *Findings in relation to literature*

Our results on progression seem not to be in line with previous reports indicating that only 37-51% of the DD patients experience progression.[11, 13, 14] For individual progression we showed that 84-89% of the participants had progression. However, if we apply a staging system similar to that of the cited studies, we would report a progression rate of 26% after 5 years of follow-up. Note that the duration of follow-up was different in the previous studies, and that two of the previous studies report progression in a clinical population only,[11, 14] possibly explaining the difference in progression rates.

The published interim analysis of this study showed that 44-95% of the participants did not have progression.[21] The difference with the current findings can be explained by the longer follow-up time, increasing the chance to capture progression.

To our surprise we found that none of the DD risk factors reported in the literature were identified as predictor for progression. This indicates that risk factors for getting the disease

are not prognostic of disease course. What surprised us even more, was that none of the previously reported DD diathesis factors we evaluated (familial occurrence of DD, ectopic lesions, early age of onset, male sex)[22, 23] were identified as predictor of progression in our cohort, while it is often suggested that patients having diathesis characteristics will have a rapidly progressive disease course. This might be related to a difference in definition of progression. In our study, every participant who had a positive yearly increase in area/TPED was labelled as having progression. Other studies used recurrence after treatment as definition for progression,[23, 24] thereby including a different part of the disease spectrum. Furthermore, by including only clinical populations, these previous studies may represent possible bias. Our study shows, based on a mixture of subclinical and clinical patients, that these variables are not strongly associated, indicating that subclinical patients share diathesis characteristics with clinical patients. Furthermore, DD diathesis factors were not associated with the histological staging,[25] partly confirming our results. Nevertheless, new biological and medical hypotheses should be posed and subsequent research should be conducted, to help understand DD progression better.

***Strengths and limitations***

We were able to describe the year-to-year disease course of DD. The prospective nature of this study limits the chance of missing values, which is often a problem in retrospective database or patient file studies. Additionally, the frequent follow-up measurements enabled a reliable estimation of the exact disease course ($R^2$ 87.0-94.2% for area, 84.0-92.0% for TPED).

Another strength is that we used area of nodules and cords to measure disease extent. In contrast to previous studies that recorded outcomes such as “progression to bilateral disease” or “progression from nodules to cords”, or defined progression as a change in disease stage,[11-14] we were able to quantify disease extent and thereby follow the disease course in participants with mild disease, without contractures. It should be noted, however, that area of nodules and cords has no clinical relevance, since patients are usually referred to the plastic surgeon when contractures are present.

Although measurement bias might have occurred when data collection was taken over by another observer, we performed an agreement study to determine whether the analyses required adjustment for this.[19] Acceptable to high intraclass correlations were obtained, so it is unlikely that measurement bias played a large role in determining area and TPED. However, recall bias might have occurred in determining the risk factors, since this was gathered anamnestically. It is therefore likely that Peyronie’s disease has been underreported in our study, as physical examination of the genital area was not part of the data collection.

Drop-outs may have introduced selection bias, as it is possible that participants with mild DD were less motivated to continue long-term participation. Although we had several strategies to prevent drop-out, still a substantial amount of participants (n = 37) quit participation. However, we observed no differences in baseline disease extent and TPED between those who quit participation versus those who were still participating. Selection bias did however occur because of severe disease progression, since postoperative data of participants who developed severe contractures were excluded from the current analyses, because after treatment we could no longer observe the natural course. Furthermore,

dropped-out participants were older and more often females than those who continued participation (Supplementary Material 1).

***Relevance of the findings and future perspectives***

We found that DD is progressive, but the speed of progression varies. More importantly, none of the factors that we assessed were strongly predictive of disease progression. This indicates that when preventive treatments will be applied in the future, the DD diathesis factors may not be that important for selecting eligible patients. Our findings also show that we have limited understanding in whom progression occurs, and that we need new hypotheses about disease progression. Future research should focus on this making use of existing population-based cohort studies, as population stratification will soon become relevant when treatment preventing progression becomes available.

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Supplementary Table 1. Characteristics of the total invited population, of those who agreed to participate and those who declined participation.

| | **Total invited N = 462** | **Agreed to participate n = 258** | **Declined to participate N = 204** |
|---|---|---|---|
| Sex | | | |
| Male (%) | 308 (66.7) | 163 (63.2) | 145 (71.1) |
| Female (%) | 154 (33.3) | 95 (36.8) | 59 (28.9) |
| Population | | | |
| General (%) | 179 (38.7) | 111 (43.0) | 68 (33.3) |
| Clinical (%) | 283 (61.2) | 147 (57.0) | 136 (66.7) |
| Age (SD) | 65.2 (11.4) | 64.6 (10.5) | 66.0 (12.4) |