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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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7 8 0	3	assessing 2-year treatment effect durability
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19	ABSTRACT
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Objectives: To assess 2-year durability of joint contracture correction following collagenase
 injections for Dupuytren's disease.

Design: Prospective cohort study.

24 Setting: Orthopedic Department in Sweden.

Participants: Patients with palpable Dupuytren's cord and active extension deficit (AED)

 $\geq 20^{\circ}$ in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A

27 surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation

28 under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before

and 5 weeks after injection. Of 57 consecutive patients (59 hands), 48 patients (50 hands)

30 were examined by a hand therapist and another 4 were telephone interviewed 24-35 (mean

31 26) months after injection. The first 29 patients completed the QuickDASH activity

32 limitations scale.

Outcome measures: Proportion of treated joints with ≥20° worsening in AED from 5 weeks
to 2 years (primary), passive extension deficit (PED), QuickDASH score, and treatment

35 satisfaction.

Results: Mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2

37 years, and for the PIP joints 30°, 13° and 16°, respectively. Between 5 weeks and 2 years

38 AED of MCP or PIP joint worsened by $\geq 20^{\circ}$ in 14 hands (28%). For joints with $\geq 10^{\circ}$

39 contracture at baseline, mean (95% CI) baseline-to-2 years AED improvement was for MCP

40 49° (41-54) and for PIP 25° (17-32). At 2 years, PED was 0°-5° in 83% of MCP and 48% of

41 PIP joints. Median QuickDASH score (25th, 75th percentiles) improved from 11.4 (2.3, 21) at

42 baseline to 2.5 (0, 9) at 5 weeks (p<0.001) and 2.3 (0, 18) at 2 years (p=0.034); 83% were

43 satisfied.

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44	Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement
45	was maintained in 3 of 4 patients. Complete contracture correction was seen in more than
46	80% of the MCP but in less than half of the PIP joints.
47	
48	Strengths and limitations
49	• Indications for collagenase treatment similar to those conventionally used for surgery.
50 51	• Measurements of joint contracture outcomes at baseline and follow-up independent of the treating surgeon
52	• Use of a validated measure of nations reported activity limitations and evaluation of
53	• Ose of a valuated measure of patient-reported activity minitations and evaluation of
54	• High participation rate with 2 year outcomes date evailable for 05% of the treated hands
54	Ingit participation rate with 2-year outcomes data available for 95% of the treated hands.
55	• Limitations include a single center and moderate sample size.
56	
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58 Introduction

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.¹ Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.,¹ surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common. We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.^{2,3} With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 and 5 years,^{4;5} the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer. Because patients mainly have activity limitations rather than symptoms, measuring patient-

reported activity limitations is important in evaluating treatment outcomes. No studies have evaluated outcomes of collagenase treatment with regard to activity limitations up to 2 years after treatment. The purpose of this study was to determine the durability of collagenase efficacy with regard to joint contractures and activity limitations 2 years after injections.

Patients and methods

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85	Study design and eligibility criteria
86	We conducted a prospective cohort study at one orthopedic department in Southern Sweden.
87	The department is the only center that treats patients with Dupuytren's disease in a region
88	with 300,000 inhabitants. The indication for treatment with collagenase injections was
89	presence of a palpable cord and a total extension deficit of $\geq 20^{\circ}$ in the MCP joint and/or PIP
90	joint. All patients who had received at least one injection and reached 2 years after first
91	injection from November 2013 through October 2014 were eligible.
92	
93	Patients
94	From September 2011 through October 2012, we treated 57 consecutive patients (59 hands)
95	with collagenase injections. In the 2 bilaterally treated patients the interval between treatments
96	was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up
97	examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not
98	participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands)
99	declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50
100	hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median
101	25, range 24 to 35) months after first injection (Table 1).
102	
103	Intervention
104	A hand surgeon injected collagenase into the cord using a modification of the standard
105	technique. ² After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all

- reconstituted collagenase (0.80 mg) into in the cord, distributed in 3 or 4 spots along the
- palpable cord, from the PIP joint to the palmar crease. After injection, a nurse applied a soft

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108 dressing and the hand therapist gave the patient verbal and written instructions regarding109 edema prophylaxis and avoidance of heavy use of the hand.

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111 The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as 112 schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine 113 buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal 114 to the collagenase injection sites) to block the nerves to the treated finger. After about a 20-115 minute interval the surgeon performed finger manipulation by applying pressure with the 116 thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into 117 maximum possible extension. 118 119 Immediately after finger manipulation, the patients went to the hand therapist and received a 120 static splint with maximally extended fingers; the therapist gave instructions on range of 121 motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 122 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case 123 contracture correction was incomplete and the patient was willing to receive further treatment, 124 the surgeon scheduled the patient for a second injection.

125

126 Measurements

127 Before treatment, one of three hand therapists measured active extension deficit (AED) in the

fingers with a goniometer and recorded the results in a standardized protocol. The first 29

- 129 patients in the study completed the 11-item disabilities of the arm, shoulder and hand
- 130 (QuickDASH) scale.⁶ At 5 weeks after injection, a hand therapist measured AED in the
- 131 fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand
- 132 therapist contacted the patients and asked them to attend the hospital for a physical

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133	examination. During this visit, the therapist measured AED as well as passive extension
134	deficit (PED) in the fingers and examined the hand for possible treatment-related
135	complications. The therapist asked the patients to report any symptoms from the treated hand
136	and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients
137	completed the QuickDASH. The same hand therapist (AL) examined all patients who
138	attended the 2-year follow-up evaluation and telephone-interviewed patients who did not
139	attend examination. During the telephone interview, the therapist asked the patients whether
140	they believed their treated finger had worsened since the 5-week follow-up visit and whether
141	they were satisfied with the results. Two of the patients interviewed by telephone also
142	completed the QuickDASH.
143	
144	We reviewed the electronic records of all participants and non-participants to ascertain any
145	subsequent surgery or other procedures on the study hand. We also recorded the number of
146	any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).
147	
148	Statistical analysis
149	The primary outcome was worsening of $\geq 20^{\circ}$ in AED from 5 weeks to 2 years. We
150	considered this cut-off as clinically important because it has been used in the previous
151	collagenase multicenter study. ⁴ In that study, recurrence or nondurability ($\geq 20^{\circ}$ increase in
152	PED in fully or partially corrected joints with presence of palpable cord, or subsequent
153	treatment) among 924 joints was 24% at 2 years. We estimated that approximately 50 patients
154	would be eligible and a 70% participation rate. With 80% power and 5% significance level, a
155	sample of 30 patients can show treatment effect durability among 75% of the patients. We
156	present the data as means with standard deviations or 95% confidence intervals and/or
157	medians with 25 th and 75 th percentiles as appropriate. We calculated the extension deficit

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158	values for MCP and PIP joints for all treated fingers and for joints that had at least 10°
159	pretreatment AED. We considered hyperextension as 0° extension deficit. We also calculated
160	total (MCP+PIP) extension deficit. Because previous studies defined complete correction as
161	PED value 0° to 5° , ^{1;4} we also analyzed the data according to this definition. This was
162	possible only for the 2-year values, because we measured only AED at baseline and 5 weeks.
163	For one patient who had surgery on the treated finger 23 months after injection we used the
164	extension deficit recorded immediately before surgery as the 2-year value in all analyses. The
165	change in AED between evaluation times (baseline, 5 weeks and 2 years) was statistically
166	tested with the paired t-test. We used the Mann-Whitney test to compare baseline and 5-week
167	AED in joints that showed $\geq 20^{\circ}$ AED worsening between 5 weeks and 2 years and joints that
168	had not worsened after a single injection. We tested the change in QuickDASH scores with
169	the Wilcoxon test (one score for both hands for the 2 bilaterally treated patient). We analyzed
170	the correlation between the changes (baseline to 2 years) in total AED and QuickDASH
171	scores with the Pearson correlation coefficient (r). We also analyzed change in total AED and
172	the QuickDASH scores according to patient satisfaction using the independent t-test and
173	analysis of covariance adjusting for sex and age. A 2-sided p-value of less than 0.05 indicated
174	statistical significance.

2 3	175	Results
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6 7	177	Toint contractions
8 9	1//	Joint contracture
10 11	178	Active extension deficit: The mean AED for the MCP joints was 54° before injection, 6° at 5
12 13	179	weeks and 9° at 2 years and the corresponding values for the PIP joints were 30°, 13° and 16°,
14 15	180	respectively (Table 2). Between 5 weeks to 2 years mean total AED had worsened by 6°, but
16 17	181	this did not reach statistical significance. From the 5-week to the 2-year follow-up, AED had
18 19	182	worsened by $\geq 20^{\circ}$ in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a
20 21 22	183	single injection). Comparison of the baseline and 5-week AED in joints that had worsened by
22 23 24	184	$\geq 20^{\circ}$ AED between 5 weeks and 2 years and those that had not worsened showed significant
25 26	185	differences for the PIP but not for the MCP joints (Table 3). A larger proportion of PIP than
27 28	186	MCP joints showed either persistent or increased AED (Figure 1). Total AED had worsened
29 30	187	by $\geq 30^{\circ}$ in 8 of the 50 hands (16%; all had received a single injection). Considering only
31 32 33	188	joints with a pretreatment AED $\geq 10^{\circ}$ (47 MCP joints [mean 57°, SD 19] and 31 PIP joints
34 35	189	[mean 48°, SD 21]), mean improvement in AED from baseline was for the MCP joints 49°
36 37	190	(95% CI 41-54, p<0.001) and for the PIP joints 25° (95% CI 17-32, p<0.001).
38 39	191	
40 41	192	Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection,
42 43 44	193	PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%).
45 46	194	A total PED \geq 30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the
47 48	195	MCP joints was 3.2° (SD 9; median 0; 25 th and 75 th percentiles 0, 0) and for the PIP joints
49 50	196	was 11° (SD 19; median 0, percentiles 0, 20).
51 52	197	
55 55	198	Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported
56 57 58 59	199	worsening of their treated finger since the 5 week follow-up.

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200	Activity limitations
201	Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1
202	had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the
203	remaining 27 patients (28 hands) the median score (25 th , 75 th percentiles) at baseline was
204	11.4 (2.3, 21), at 5 weeks 2.5 (0, 9) and at 2 years 2.3 (0, 18). Changes from baseline to 5
205	weeks and to 2 years were statistically significant (p<0.001 and p=0.034, respectively) but not
206	changes from 5 weeks to 2 years (p=0.45). The correlation between baseline to 2 years
207	changes in total AED and QuickDASH score was moderate (r=0.49, p=0.010). For all 49
208	patients who completed the QuickDASH at 2 years, the median score was 2.5 (0, 18).
209	
210	Patient satisfaction
211	The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4
212	hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in
213	total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among
214	"dissatisfied" patients was 39 (SD 36); adjusted mean difference 24 (95% CI, 3-45, p=0.027).
215	Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for the

216 dissatisfied patients 1 (SD 25); adjusted mean difference -9 (95%, CI -24-6, p=0.25). Mean 2-

217 year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied"

218 patients 26 (SD 13); adjusted mean difference -16 (95% CI -27-5, p=0.007).

220 Subsequent surgery and adverse events

221 One patient had recurrent MCP contracture after 1 injection and chose to have limited

fasciectomy, which was done 23 months after injection. No other patients had surgery or

223 needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not

224 observe and the patients did not report any treatment-related adverse events.

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Discussion

227	This prospective cohort study of patients with Dupuytren's disease treated with collagenase
228	injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4
229	patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients
230	who did not respond also were dissatisfied), possibly because of incomplete initial correction
231	or recurrent contracture in the treated finger. Considering its relative simplicity compared to
232	fasciectomy the results of this the 2-year treatment effect durability assessment support the
233	continued use of collagenase injection as an effective treatment option in patients with
234	Dupuytren's disease. Assuming hypothetically that all patients with $\geq 30^{\circ}$ total PED at 2 years
235	would receive a new injection, implying almost a third of all patients require 2 injections, the
236	treatment costs would still be lower compared to surgery. ² The comparison involves only
237	direct treatment costs; it does not take into consideration the costs of possible surgical
238	complications. ² Because patients who have good results may still experience worsening after
239	2 years, a new assessment is necessary with longer follow-up.
240	
241	Most patients received a single injection but about 10% of the patients needed a second
242	injection because the initial reduction was inadequate. Similar to previous studies of both
243	collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80%
244	of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints
245	that had worsened after the 5-week follow-up had more severe contracture both before
246	treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints.
247	This may suggest that in case the first injection fails to achieve adequate correction for PIP
248	joints the surgeon should consider a second injection early. This question needs further study.
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250 Comparison with other collagenase studies

We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2 years to facilitate comparison with previous studies. With regard to joint contracture, passive deficit would be equal or less than active deficit. Thus, our posttreatment AED values are conservative when compared to studies that reported posttreatment PED values.

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In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS), 621 of 950 (65%) of the initial study participants could be followed.⁴ The authors defined "recurrence" as contracture worsening by $\geq 20^{\circ}$ combined with presence of palpable cord or further treatment including injection, in successfully treated joints (0° to 5° extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which treatment had failed initially were excluded. Same definition applied to partially corrected joints (improved by $\geq 20^{\circ}$) was classified as "nondurability". At 2 years, recurrence had occurred in 20% and nondurability in 33%. Contracture "worsening" (defined as $\geq 20^{\circ}$ increase in contracture in fully or partially corrected joints with or without palpable cord or subsequent treatment) at 3 years was 28% for MCP and 58% for PIP; no 2-year data were reported. The study reported that for successfully treated MCP joints mean PED at baseline was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20 (SD 19), respectively,⁴ and a substantial number of patients received multiple injections. In our study, mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19), respectively. Because we measured PED only at 2 years, it is not possible to make a direct comparison with the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32 hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie

274 "successfully treated" according to CORDLESS definition), 2 had PED $\geq 20^{\circ}$ at 2 years and 1

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275	had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS.
276	This is an overestimate because the CORDLESS patients had to have both contracture
277	worsening and palpable cord to be considered as recurrence and a large number of different
278	surgeons recorded presence of palpable cord (validity uncertain). Although it is difficult to
279	compare results because of differences in definitions, our results appear to be more favorable.
280	Comparison with limited fasciectomy and percutaneous needle fasciotomy
281	Although many studies have reported fasciectomy results, ⁷ we believe only prospective
282	studies with high follow-up participation can provide good-quality outcomes data. A recent
283	prospective study of 90 patients treated with limited fasceictomy at a university hand surgery
284	center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and
285	for the PIP joints 22 (SD 18). ⁸ It is unclear whether the authors used 0° for hyperextension (as
286	in our study) or used the actual values, which would underestimate the reported extension
287	deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results
288	compare favorably with the 1-year results after limited fasciectomy. Surgery-related
289	complications reported in the study included nerve injury (4 patients) and complex regional
290	pain syndrome (4 patients) and many patients required extensive therapy. ⁸ Collagenase
291	treatment does not require extensive hand therapy. Almost all patients required only two hand
292	therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).
293	
294	In a randomized study that defined recurrence after needle fasciotomy as $\geq 30^{\circ}$ worsening in
295	the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had
296	recurrence. ⁹ Applying the same definition to our study but using total AED, 8 of 50 hands
297	(16%) would be defined as having recurrence.
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299	The Swedish National Quality Register for Hand Surgery have reported outcome data for
300	patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments
301	between 2010 and 2014. ¹⁰ The mean DASH score in patients treated with collagenase had
302	improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for
303	limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52)
304	and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to
305	100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was
306	79%, and after closed fasciotomy (n=73) was 69% . ¹⁰
307	
308	We do not use the outcome "recurrence" because of lack of consensus about the definition of
309	recurrence. Treatment with collagenase inherently implies that part of the cord is left intact
310	and therefore it would be impossible to know with acceptable certainty whether a presence of
311	a cord is indicative of recurrence. We believe the degree of joint contracture before and after
312	treatment is a more valid measure of outcome irrespective of whether the cause of the
313	contracture is incomplete correction, disease recurrence/progression, or other cause.
314	
315	Activity limitations
316	We used the QuickDASH as patient-reported measure of activity limitations and the results
317	show that the scores improved significantly after treatment. The magnitude of improvement
318	differed according to changes in joint contracture and with patient satisfaction. These findings
319	support the use of the QuickDASH in DC. Because the median pretreatment QuickDASH
320	score was relatively low, it may not be appropriate in studies comparing different treatments
321	because it would be difficult to detect important between-group differences. However, in
322	patients with DC, no thresholds have been established for within-group and between-group
323	differences in QuickDASH score to be considered as clinically important. Besides, it is not

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obvious that the same threshold should apply to complex treatments that include surgery and
extensive rehabilitation as to less invasive treatments that are associated with substantially
lower risks and burden on patients.

327

328 The limitations of our study include a single center and a moderate sample size, implying

329 uncertain generalizability. We did not measure passive but only active extension deficit at

baseline and at 5 weeks after injection and only the first 29 patients completed the

331 QuickDASH. Further, patients stated whether they were satisfied or not satisfied with the

332 results; a scale with more response options may have yielded different results. Our study has

333 several strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2

334 years, independent of the treating surgeon, and a validated scale used to measure patient-

335 reported activity limitations. The high participation rate is a major strength with 2-year

336 outcomes data available for 95% of the treated hands of patients still living.

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370	Acknowledgments
371	This study was supported by the Departments of Orthopedics and Rehabilitation, Hässleholm
372	and Kristianstad Hospitals, and Region Skåne, Sweden.
373	
374	Contributors
375	AL: contributed to study design, collected the data, assisted in the analysis and interpretation
376	of the data, contributed to drafting of the manuscript, and approved the final version
377	submitted for publication.
378	IA: led the project, designed the study, conducted data analysis and interpretation, contributed
379	to drafting of the manuscript, and approved the final version submitted for publication.
380	
381	Ethics approval
382	This research was approved by the Regional Ethical Review Board in Lund (Dnr 2013/656)
383	and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000.
384	
385	Competing interests
386	IA was a member of an Expert Group on Dupuytren's disease for Pfizer in 2012 and
387	participated in meetings organized by Sobi in 2014 and 2015.
388	
389	Funding
390	No external funding.
391	
392	Data sharing statement
393	No additional data available.
394	

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395 Figure legend

397	Figure 1. Active extension deficit (AED) for the metacarpophalangeal (MCP) and proximal
398	interphalangeal (PIP) joints 5 weeks and 2 years after collagenase injection for Dupuytren's
399	contracture in 50 treated fingers. The joints shown in this diagram are those with AED of at
400	least 10° at 5 weeks or in which AED had changed between 5 weeks and 2 years; AED
401	measured with 5° intervals and joints with identical values juxtaposed for visual clarity. In 4
402	joints a second injection after the 5-week measurement was given. Joints without contracture
403	(AED 0° to 5°) at both evaluation times (27 MCP and 23 PIP joints) are not shown in the
404	diagram.
405	

Table 1. Characteristics of the participants and non-participants in the 2-year follow-up physical examination
Participants Non-participants

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38:12	8:1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34 : 16	8:1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5:3:1:0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit ^{\dagger}		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

⁸ *Interval: 4 weeks (1 patient), 2 months (1 patient), 6 months (3 patients), all 5 had MCP and PIP contracture at

409 baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP

410 correction).

411 [†]Median (25th, 75th percentiles) active extension deficit of the metacarpophalangeal and proximal interphalangeal

412 joints of the treated finger.

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414	Table 2. Activ	Table 2. Active extension deficit before and after collagenase injection for Dupuytren's disease						
		Baseline	5 wk	2 yr	Mean differer	nce (95%	CI), p-value	
		n = 50	n = 50	n = 50	Baseline to 2	yr	5 wk to 2 yr	
	МСР	54 (23)	6 (12)	9 (16)	45 (38 to 52)	< 0.001	-3.1 (-7.8 to 1.6)	0.20
	PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20)	< 0.001	-3.3 (-6.7 to 0.1)	0.05
	MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68)	< 0.001	-6.4 (-12 to -0.06)	0.03
415 416	MCP, metaca	rpophalange	al joint; PI	P, proxima	l interphalangea	l joint		

- 417 Table 3. Baseline and 5-week active extension deficit for the joints
- 418 that had worsened by $\geq 20^{\circ}$ and the joints that had not worsened between
- 419 5 weeks and 2 years after a single collagenase injection

	Worsened	Not worsened	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 weeks	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 weeks	15 (15, 55)	0 (0, 15)	0.004

421 Values are median (25th, 75th percentile)

422 MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint



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STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	P1,2	(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found
	P2,3	
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P 4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P 5	Present key elements of study design early in the paper
Setting	5 P5	Describe the setting, locations, and relevant dates, including periods of recruitment,
		exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
	P5,6	selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of
		selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of
		controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
	P6,7	modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement	P6,7	assessment (measurement). Describe comparability of assessment methods if there
		is more than one group
Bias	9 P7 ,8	Describe any efforts to address potential sources of bias
Study size	10 <mark>P7</mark>	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
	P7,8	describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
	P7,8	(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of
		sampling strategy
		(<u>e</u>) Describe any sensitivity analyses
Continued on next next		

Continued on next page

Page	25	of	25
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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially
	P5 &	eligible, examined for eligibility, confirmed eligible, included in the study, completing
	T 1	follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
data	T 1	information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) Cohort study—Summarise follow-up time (eg, average and total amount)
Outcome data	15* <mark>P9-</mark>	Cohort study-Report numbers of outcome events or summary measures over time
	11, T2,	Case-control study—Report numbers in each exposure category, or summary measures
	Fig	of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 <mark>P9-11</mark> ,	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
	T2	their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period
Other analyses	17 P9,10	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity
		analyses
Discussion		
Key results	18 P11	Summarise key results with reference to study objectives
Limitations	19 P14	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other information	on	
Funding	22 P 17	Give the source of funding and the role of the funders for the present study and, if
-		applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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Primary Subject Heading :	Surgery
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Hand & wrist < ORTHOPAEDIC & TRAUMA SURGERY, Dupuytren, Collagenase



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1	Collagenase injections for Dupuytren's disease: prospective cohort study
2	assessing 2-year treatment effect durability
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18	ABSTRACT
19	

20 Objectives: To assess 2-year durability of joint contracture correction following collagenase
21 injections for Dupuytren's disease.

Design: Prospective cohort study.

- 23 Setting: Orthopedic Department in Sweden.
- **Participants:** Patients with palpable Dupuytren's cord and active extension deficit (AED)
- $25 \geq 30^{\circ}$ in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A
- 26 surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation
- 27 under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before
- and 5 weeks after injection in all treated patients. Of 57 consecutive patients (59 hands), 48
- 29 patients (50 hands) were examined by a hand therapist 24-35 (mean 26) months after
- 30 injection. Five of the patients had received a second injection in the same finger within 6
- 31 months of the first injection.

Outcome measures: Primary outcome was proportion of treated joints with $\geq 20^{\circ}$ worsening

- in AED from 5 weeks to 2 years.
- **Results:** Mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2
- 35 years, and for the PIP joints 30°, 13° and 16°, respectively. Between the 5-week and 2-year
- 36 measurements AED of MCP or PIP joint worsened by $\geq 20^{\circ}$ in 14 hands (28%). For joints
- 37 with $\geq 10^{\circ}$ contracture at baseline, mean (95% CI) baseline-to-2 years AED improvement was
- 38 for MCP 49° (41-54) and for PIP 25° (17-32). No treatment-related adverse events were
- 39 observed at the 2-year follow-up evaluation.
- 40 Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement
- 41 was maintained in 72% of the treated hands. Complete contracture correction was seen in
- 42 more than 80% of the MCP but in less than half of the PIP joints.

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43	St	rengths and limitations
44	•	Indications for collagenase treatment similar to those conventionally used for surgery.
45	•	Measurements of joint contracture outcomes at baseline and follow-up independent of the
46		treating surgeon.
47	•	Use of an upper-extremity specific measure of patient-reported activity limitations
48		(QuickDASH) and evaluation of patient satisfaction.
49	•	High participation rate with 2-year outcomes data available for 95% of the treated hands.
50	•	Limitations include a single center, moderate sample size, lack of 12-month follow-up,
51		QuickDASH administered to only a subgroup of patients at baseline, QuickDASH not
52		validated specifically in patients with Dupuytren's disease, and use of binary patient
53		satisfaction item.
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56 INTRODUCTION

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.^{1,2} Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.¹ surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common.³ We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.^{4,5} With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 years and 5 years,^{6,7} the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer. Because patients mainly have activity limitations rather than symptoms, measuring patient-reported activity limitations is important in evaluating treatment outcomes. Little is known about outcomes of collagenase treatment with regard to activity limitations up to 2 years after

79 treatment. The purpose of this study was to determine the durability of collagenase efficacy

80 with regard to joint contractures and activity limitations 2 years after injections.

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PATIENTS AND METHODS

Study design and eligibility criteria

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only center that treats patients with Dupuytren's disease in a region with 300,000 inhabitants. The indication for treatment with collagenase injections was presence of a palpable cord and a total extension deficit of $\geq 20^{\circ}$ in the MCP joint and/or PIP joint. All patients who had received at least one injection and reached 2 years after first injection from November 2013 through October 2014 were eligible.

Patients

From September 2011 through October 2012, we treated 57 consecutive patients (59 hands) with collagenase injections. In the 2 bilaterally treated patients the interval between treatments was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands) declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50 hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median

25, range 24 to 35) months after first injection (Table 1).

Intervention

- A hand surgeon injected collagenase into the cord using a modification of the standard
- technique.⁴ After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all
- reconstituted collagenase that could be withdrawn (approximately 0.80 mg) in the cord,
- distributed in 3 or 4 spots along the palpable cord, from the PIP joint to the palmar crease.

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After injection, a nurse applied a soft dressing and the hand therapist gave the patient verbal
and written instructions regarding edema prophylaxis and avoidance of heavy use of the hand.

The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal to the collagenase injection sites) to block the nerves to the treated finger. After about a 20minute interval the surgeon performed finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into

- 115 maximum possible extension.
- 116

Immediately after finger manipulation, the patients went to the hand therapist and received a static splint with fingers in maximal possible extension; the therapist gave instructions on edema management, range of motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case contracture correction was incomplete and the patient was willing to receive further treatment, the surgeon scheduled the patient for a second injection.

123

124 Measurements

125 Before treatment, one of three hand therapists measured active extension deficit (AED) in the

- fingers with a goniometer and recorded the results in a standardized protocol. The first 29
- 127 patients in the study completed the 11-item disabilities of the arm, shoulder and hand
- 128 (QuickDASH) scale.⁸ At 5 weeks after injection, a hand therapist measured AED in the
- 129 fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand
- 130 therapist contacted the patients and asked them to attend the hospital for a physical

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131	examination. During this visit, the therapist measured AED as well as passive extension
132	deficit (PED) in the fingers and examined the hand for possible treatment-related
133	complications. The therapist asked the patients to report any symptoms from the treated hand
134	and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients
135	completed the QuickDASH. The same hand therapist (AL) examined all patients who
136	attended the 2-year follow-up evaluation and telephone-interviewed patients who did not
137	attend examination. During the telephone interview, the therapist asked the patients whether
138	they believed their treated finger had worsened since the 5-week follow-up visit and whether
139	they were satisfied with the results. Two of the patients interviewed by telephone also
140	completed the QuickDASH.
141	
142	We reviewed the electronic records of all participants and non-participants to ascertain any
143	subsequent surgery or other procedures on the study hand. We also recorded the number of
144	any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).
145	
146	Statistical analysis
147	Sample size: The primary outcome was worsening of $\geq 20^{\circ}$ in AED between the 5-week and
148	the 2-year measurements. We considered this cut-off as clinically important because it has
149	been used in the previous collagenase multicenter study. ⁶ In that study, recurrence or
150	nondurability (≥20° increase in PED in fully or partially corrected joints with presence of
151	palpable cord, or subsequent treatment) among 924 joints was 24% at 2 years. We estimated
152	that approximately 50 patients would be eligible and a 70% participation rate. With 80%
153	power and 5% significance level, a sample of 30 patients can show treatment effect durability
154	among 75% of the patients.

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155	Primary analysis: We recorded AED values for MCP and PIP joints for all treated fingers at 3
156	measurement times (baseline, 5 weeks and 2 years) and calculated the proportion of fingers
157	that showed worsening of $\geq 20^{\circ}$ in AED from the 5-week to the 2-year measurements.
158	Secondary analyses: In addition to AED values for all MCP and PIP joints and total
159	(MCP+PIP) extension deficit in the treated fingers we analyzed AED values for joints that
160	had at least 10° pretreatment AED. We considered hyperextension as 0° extension deficit.
161	Because previous studies defined complete correction as PED value 0° to 5°, ^{1,6} we also
162	analyzed the data according to this definition. This was possible only for the 2-year values,
163	because we measured only AED at baseline and 5 weeks. The change in AED between
164	evaluation times (baseline, 5 weeks and 2 years) was statistically tested with the paired t-test.
165	We used the Mann-Whitney test to compare baseline and 5-week AED in joints that showed
166	\geq 20° AED worsening between the 5-week and 2-year measurements and joints that had not
167	worsened after a single injection. We tested the change in QuickDASH scores with the
168	Wilcoxon test (one score for both hands for the 2 bilaterally treated patients). We analyzed the
169	correlation between the changes (baseline to 2 years) in total AED and QuickDASH scores
170	with the Pearson correlation coefficient (r). We also analyzed treatment satisfaction according
171	to changes in total AED and QuickDASH scores using analysis of covariance adjusting for
172	sex, age and baseline total AED or QuickDASH score, respectively. We did a similar analysis
173	for the 2-year QuickDASH scores adjusting for sex and age.
174	
175	We present the data as proportions, means with standard deviations or 95% confidence
176	intervals, and/or medians with 25 th and 75 th percentiles as appropriate. For one patient who
177	had surgery on the treated finger 23 months after injection we used the extension deficit
178	recorded immediately before surgery as the 2-year value in all analyses. A 2-sided p-value of
179	less than 0.05 indicated statistical significance.

181

182

RESULTS

Joint contracture

1

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183	Active extension deficit: Between the 5-week and the 2-year measurements, AED had
184	worsened by $\geq 20^{\circ}$ in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a
185	single injection). For all treated fingers, the mean AED for the MCP joints was 54° before
186	injection, 6° at 5 weeks and 9° at 2 years and the corresponding values for the PIP joints were
187	30°, 13° and 16°, respectively (Table 2). Between the 5-week and 2-year measurement mean
188	total AED had worsened by 6°, but this did not reach statistical significance.
189	
190	Comparison of the baseline and 5-week AED in joints that had worsened by $\geq 20^{\circ}$ AED
191	between the 5-week and the 2-year measurements and those that had not worsened showed
192	significant differences for the PIP but not for the MCP joints (Table 3). The difference was
193	large for the baseline AED but smaller for the 5-week AED. Thus, PIP joints with a large
194	pretreatment AED and incomplete initial correction were more likely to worsen between the
195	5-week and 2-year measurements than joints with less severe contracture and good initial
196	correction, but this was not the case for MCP joints.
197	
198	A larger proportion of PIP than MCP joints showed either persistent or increased AED (figure
199	1). Total AED had worsened by $\geq 30^{\circ}$ in 8 of the 50 hands (16%; all had received a single
200	injection). Considering only joints with a pretreatment AED $\geq 10^{\circ}$ (47 MCP joints [mean 57°,
201	SD 19] and 31 PIP joints [mean 48°, SD 21]), mean improvement in AED from baseline was
202	for the MCP joints 49° (95% CI 41 to 54, p<0.001) and for the PIP joints 25° (95% CI 17 to
203	32, p<0.001).
	10
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205	Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection,
206	PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%).
207	A total PED \geq 30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the
208	MCP joints was 3.2° (SD 9; median 0; 25 th and 75 th percentiles 0, 0) and for the PIP joints
209	was 11° (SD 19; median 0, percentiles 0, 20).
210	
211	Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported
212	worsening of their treated finger since the 5 week follow-up.
213	
214	Activity limitations
215	Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1
216	had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the
217	remaining 27 patients (28 hands) the median score (25 th , 75 th percentiles) at baseline was 11
218	(2, 21), at 5 weeks 3 (0, 9) and at 2 years 2 (0, 18). Changes from baseline to 5 weeks and to 2
219	years were statistically significant (p<0.001 and p=0.034, respectively) but not changes from
220	5 weeks to 2 years (p=0.45). The correlation between baseline to 2 years changes in total
221	AED and QuickDASH score was moderate (r=0.49, p=0.010). For all 49 patients who
222	completed the QuickDASH at 2 years, the median score was 3 (0, 18).
223	
224	Patient satisfaction
225	The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4
226	hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in
227	total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among
228	"dissatisfied" patients was 39 (SD 36); adjusted mean difference 37 (95% CI 26 to 49,
229	p<0.001). Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for

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2 3 4	230	the dissatisfied patients 1 (SD 25); adjusted mean difference -12 (95% CI -23 to -2, p=0.047).
5 6	231	Mean 2-year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied"
7 8	232	patients 26 (SD 13); adjusted mean difference -16 (95% CI -27 to -5, p=0.007).
9 10 11	233	
12 13	234	Subsequent surgery and adverse events
14 15	235	One patient had recurrent MCP contracture after 1 injection and chose to have limited
16 17	236	fasciectomy, which was done 23 months after injection. No other patients had surgery or
18 19 20	237	needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not
20 21 22	238	observe and the patients did not report any treatment-related adverse events.
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DISCUSSION

241	This prospective cohort study of patients with Dupuytren's disease treated with collagenase
242	injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4
243	patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients
244	who did not respond also were dissatisfied), possibly because of incomplete initial correction
245	or recurrent contracture in the treated finger. Considering its relative simplicity compared to
246	fasciectomy the results of this the 2-year treatment effect durability assessment support the
247	continued use of collagenase injection as an effective treatment option in patients with
248	Dupuytren's disease. Assuming hypothetically that all patients with $\geq 30^{\circ}$ total PED at 2 years
249	would receive a new injection, implying almost a third of all patients require 2 injections, the
250	treatment costs would still be lower compared to surgery. ² The comparison involves only
251	direct treatment costs; it does not take into consideration the costs of possible surgical
252	complications. ² Because patients who have good results may still experience worsening after
253	2 years, a new assessment is necessary with longer follow-up.
254	
255	Most patients received a single injection but about 10% of the patients needed a second
256	injection because the initial reduction was inadequate. Similar to previous studies of both
257	collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80%
258	of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints
259	that had worsened after the 5-week follow-up had more severe contracture both before
260	treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints.
261	This may suggest that in case the first injection fails to achieve adequate correction for PIP
262	joints the surgeon should consider a second injection early. This question needs further study.
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2 3 4	264	Comparison with other collagenase studies
- 5 6	265	We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2
7 8	266	years to facilitate comparison with previous studies. With regard to joint contracture, passive
9 10	267	deficit would be equal or less than active deficit. Thus, our posttreatment AED values are
11 12 12	268	conservative when compared to studies that reported posttreatment PED values.
13 14 15	269	
16 17	270	In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study
18 19	271	(CORDLESS), 621 of 950 (65%) of the initial study participants could be followed. ⁶ The
20 21	272	authors defined "recurrence" as contracture worsening by $\geq 20^{\circ}$ combined with presence of
22 23 24	273	palpable cord or further treatment including injection, in successfully treated joints (0° to 5°
24 25 26	274	extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which
27 28	275	treatment had failed initially were excluded. Same definition applied to partially corrected
29 30	276	joints (improved by $\geq 20^{\circ}$) was classified as "nondurability". At 2 years, recurrence had
31 32 32	277	occurred in 20% and nondurability in 33%. Contracture "worsening" (defined as $\geq 20^{\circ}$
33 34 35	278	increase in contracture in fully or partially corrected joints with or without palpable cord or
36 37	279	subsequent treatment) at 3 years was 28% for MCP and 58% for PIP; no 2-year data were
38 39	280	reported. The study reported that for successfully treated MCP joints mean PED at baseline
40 41	281	was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20 (SD 19),
42 43 44	282	respectively, ⁶ and a substantial number of patients received multiple injections. In our study,
44 45 46	283	mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19), respectively.
47 48	284	
49 50	285	Because we measured PED only at 2 years, it is not possible to make a direct comparison with
51 52	286	the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32
53 54 55	287	hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie
56 57 58	288	"successfully treated" according to CORDLESS definition), 2 had PED $\geq 20^{\circ}$ at 2 years and 1

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289	had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS.
290	This is an overestimate because the CORDLESS patients had to have both contracture
291	worsening and palpable cord to be considered as recurrence and a large number of different
292	surgeons recorded presence of palpable cord (validity uncertain). Although it is difficult to
293	compare results because of differences in definitions, our results appear to be more favorable.
294	A study of 47 patients with 1 MCP contracture (30°-60°) and no PIP contracture, treated with
295	a single 0.58-mg collagenase injection, reported a 25% 2-year recurrence (>20° contracture). ⁹
296	
297	Comparison with limited fasciectomy and percutaneous needle fasciotomy
298	Although many studies have reported fasciectomy results, ¹⁰ we believe only prospective
299	studies with high follow-up participation can provide good-quality outcomes data. A recent
300	prospective study of 90 patients treated with limited fasciectomy at a university hand surgery
301	center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and
302	for the PIP joints 22 (SD 18). ¹¹ It is unclear whether the authors used 0° for hyperextension
303	(as in our study) or used the actual values, which would underestimate the reported extension
304	deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results
305	compare favorably with the 1-year results after limited fasciectomy. Surgery-related
306	complications reported in the study included nerve injury (4 patients) and complex regional
307	pain syndrome (4 patients) and many patients required extensive therapy. ¹¹ Collagenase
308	treatment does not require extensive hand therapy. Almost all patients required only two hand
309	therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).
310	
311	In a randomized study that defined recurrence after needle fasciotomy as $\ge 30^{\circ}$ worsening in
312	the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had

1		
2 3	313	recurrence. ¹² Applying the same definition to our study but using total AED, 8 of 50 hands
4 5 6	314	(16%) would be defined as having recurrence.
7 8	315	
9 10	316	The Swedish National Quality Register for Hand Surgery have reported outcome data for
11 12	317	patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments
13 14 15	318	between 2010 and 2014. ¹³ The mean DASH score in patients treated with collagenase had
16 17	319	improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for
18 19	320	limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52)
20 21	321	and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to
22 23	322	100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was
24 25 26	323	79%, and after closed fasciotomy (n=73) was 69%. ¹³ A Swedish 2-center randomized study of
27 28	324	collagenase versus needle fasciotomy found no differences at 1 year, but it included mainly
29 30	325	patients with only MCP contractures and the treating surgeons measured the outcomes. ¹⁴
31 32	326	
33 34 35	327	We do not use the outcome "recurrence" because of lack of consensus about the definition of
36 37	328	recurrence. Treatment with collagenase inherently implies that part of the cord is left intact
38 39	329	and therefore it would be impossible to know with acceptable certainty whether a presence of
40 41	330	a cord is indicative of recurrence. We believe the degree of joint contracture before and after
42 43	331	treatment is a more valid measure of outcome irrespective of whether the cause of the
44 45 46	332	contracture is incomplete correction, disease recurrence/progression, or other cause.
47 48	333	
49 50	334	Activity limitations
51 52	335	We used the QuickDASH as patient-reported measure of activity limitations and the results
53 54 55	336	show that the scores improved significantly after treatment. The magnitude of improvement
55 56 57	337	differed according to changes in joint contracture and with patient satisfaction. Because the
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338	median pretreatment QuickDASH score was relatively low, it may not be appropriate in
339	studies comparing different treatments because it would be difficult to detect important
340	between-group differences. However, in patients with DC, no thresholds have been
341	established for within-group and between-group differences in QuickDASH score to be
342	considered as clinically important. Besides, it is not obvious that the same threshold should
343	apply to complex treatments that include surgery and extensive rehabilitation as to less
344	invasive treatments that are associated with substantially lower risks and burden on patients.
345	
346	The limitations of our study include a single center and a moderate sample size, implying
347	uncertain generalizability. We did not measure passive but only active extension deficit at
348	baseline and at 5 weeks after injection and only the first 29 patients completed the
349	QuickDASH at these follow-up times. Another limitation is lack of 12-month follow-up.
350	Further, patients stated whether they were satisfied or not satisfied with the results at 2 years;
351	a scale with more response options may have yielded different results. Our study has several
352	strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2 years,
353	independent of the treating surgeon, and a validated scale used to measure patient-reported
354	activity limitations. The high participation rate is a major strength with 2-year outcomes data
355	available for 95% of the treated hands of patients still living.

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403	
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406	of the data, contributed to drafting of the manuscript, and approved the final version
407	submitted for publication.
408	IA: led the project, designed the study, conducted data analysis and interpretation, contributed
409	to drafting of the manuscript, and approved the final version submitted for publication.
410	
411	Ethics approval
412	This research was approved by the Regional Ethical Review Board in Lund (Dnr 2013/656)
413	and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000.
414	
415	Competing interests
416	IA was a member of an Expert Group on Dupuytren's disease for Pfizer in 2012 and has
417	participated in meetings organized by Sobi.
418	
419	Funding
420	No external funding.
421	
422	Data sharing statement
423	No additional data available.
424	

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425 Figure legend

427	Figure 1. Active extension deficit (AED) for the metacarpophalangeal (MCP) and proximal
428	interphalangeal (PIP) joints 5 weeks and 2 years after collagenase injection for Dupuytren's
429	contracture in 50 treated fingers. The joints shown in this diagram are those with AED of at
430	least 10° at 5 weeks or in which AED had changed between the 5-week and the 2-year
431	measurements; AED measured with 5° intervals and joints with identical values juxtaposed
432	for visual clarity. For example, the ♦ farthest to the right on the X-axis represents a treated
433	finger in which MCP AED was 0° at 5 weeks and 65° at 2 years, and the \Box in the upper right
434	corner of the graph represent a treated finger in which PIP AED was 55° at 5 weeks and 75°
435	at 2 years. In 4 joints a second injection after the 5-week measurement was given. Joints
436	without contracture (AED 0° to 5°) at both the 5-week and the 2-year measurement (27 MCP
437	and 23 PIP joints) are not shown in the diagram.
438	

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Table 1 Characteristics of the participants and non-participants in the 2-year follow-up physical examination

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38:12	8:1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34:16	8:1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5:3:1:0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit [†]		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP

correction).

[†]Median (25th, 75th percentiles) active extension deficit (degrees) of the metacarpophalangeal and proximal

interphalangeal joints of the treated finger. For all treated fingers, the minimum total extension deficit was 30

degrees.

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Table 2 Active extension deficit in the treated fingers immediately before collagenase injection (baseline) and at

 5 weeks and 2 years after injection.

	Baseline	5 wk	2 yr	Mean difference (95%	CI), p-value	
	n = 50	n = 50	n = 50	Baseline - 2 yr	5 wk - 2 yr	
MCP	54 (23)	6 (12)	9 (16)	45 (38 to 52) <0.001	-3.1 (-7.8 to 1.6)	0.20
PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20) <0.001	-3.3 (-6.7 to 0.1)	0.05
MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68) <0.001	-6.4 (-12 to -0.06)	0.03

451 MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

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452	Fable 3	Baseline and	5-week active	e extension	deficit fo	r the j	oints
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453 that had worsened by $\geq 20^{\circ}$ at the 2-year measurement (compared to the

454 5-week measurement) and the joints that had not worsened between these

455 two measurement times; hands treated with a single collagenase injection.

	Worsened ≥20° after the 5-week postinjection measurement	Not worsened after the 5-week postinjection measurement	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 wk	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 wk	15 (15, 55)	0 (0, 15)	0.004

Values are median (25th, 75th percentile) active extension deficit

458 MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

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figure 1 173x117mm (300 x 300 DPI)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the
	P1,2	abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
	P2,3	and what was found
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P 4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P 5	Present key elements of study design early in the paper
Setting	5 P 5	Describe the setting, locations, and relevant dates, including periods of recruitment,
		exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
	P5,6	selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of
		selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of
		controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and
	P6,7,9	effect modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement	P6,7	assessment (measurement). Describe comparability of assessment methods if there
		is more than one group
Bias	9 P7,8	Describe any efforts to address potential sources of bias
Study size	10 <mark>P7</mark>	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
	P7,8	describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
	P7,8,9	(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was
		addressed
		Cross-sectional study-If applicable, describe analytical methods taking account of
		sampling strategy
		(<u>e</u>) Describe any sensitivity analyses
Continued on next page		

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially
	P5 &	eligible, examined for eligibility, confirmed eligible, included in the study, completing
	T1	follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
data	T1	information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) Cohort study—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P9-	Cohort study-Report numbers of outcome events or summary measures over time
	11, T2,	Case-control study—Report numbers in each exposure category, or summary measures
	Fig	of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 <mark>P9-11</mark> ,	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
	T2	their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period
Other analyses	17 P9,10	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity
		analyses
Discussion		
Key results	18 <mark>P11</mark>	Summarise key results with reference to study objectives
Limitations	19 <mark>P14</mark>	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other informati	on	
Funding	22 P 17	Give the source of funding and the role of the funders for the present study and, if
		applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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1	Collagenase injections for Dupuytren's disease: prospective cohort study
2	assessing 2-year treatment effect durability
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17	

Objectives: To assess 2-year durability of joint contracture correction following collagenase

ABSTRACT

21	injections for Dupuytren's disease.
22	Design: Prospective cohort study.
23	Setting: Orthopedic Department in Sweden.
24	Participants: Patients with palpable Dupuytren's cord and active extension deficit (AED)
25	\geq 30° in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A
26	surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation
27	under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before
28	and 5 weeks after injection in all treated patients. Of 57 consecutive patients (59 hands), 48
29	patients (50 hands) were examined by a hand therapist 24-35 (mean 26) months after
30	injection. Five of the patients had received a second injection in the same finger within 6
31	months of the first injection.
32	Outcome measures: Primary outcome was proportion of treated joints with $\geq 20^{\circ}$ worsening
33	in AED from 5 weeks to 2 years.
34	Results: Between the 5-week and the 2-year measurements, AED had worsened by $\geq 20^{\circ}$ in 7
35	MCP and 7 PIP joints (28% of the treated hands; all had received a single injection). Mean
36	AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years, and for the
37	PIP joints 30°, 13° and 16°, respectively For joints with $\geq 10^{\circ}$ contracture at baseline, mean
38	(95% CI) baseline-to-2 years AED improvement was for MCP 49° (41-54) and for PIP 25°
39	(17-32). No treatment-related adverse events were observed at the 2-year follow-up
40	evaluation.
41	Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement
42	was maintained in 72% of the treated hands. Complete contracture correction was seen in
43	more than 80% of the MCP but in less than half of the PIP joints.

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44	Strengths and limitations
45	• Indications for collagenase treatment similar to those conventionally used for surgery.
46	• Measurements of joint contracture outcomes at baseline and follow-up independent of the
47	treating surgeon.
48	• Use of an upper-extremity specific measure of patient-reported activity limitations
49	(QuickDASH) and evaluation of patient satisfaction.
50	• High participation rate with 2-year outcomes data available for 95% of the treated hands.
51	• Limitations include a single center, moderate sample size, lack of 12-month follow-up,
52	QuickDASH administered to only a subgroup of patients at baseline, QuickDASH not
53	validated specifically in patients with Dupuytren's disease, and use of binary patient
54	satisfaction item.
55	
56	

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57 INTRODUCTION

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.^{1,2} Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.¹ surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common.³ We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.^{4,5} With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 years and 5 years.^{6,7} the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer. Because patients mainly have activity limitations rather than symptoms, measuring patient-reported activity limitations is important in evaluating treatment outcomes. Little is known

about outcomes of collagenase treatment with regard to activity limitations up to 2 years after

80 treatment. The purpose of this study was to determine the durability of collagenase efficacy

81 with regard to joint contractures and activity limitations 2 years after injections.

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PATIENTS AND METHODS

Study design and eligibility criteria

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only center that treats patients with Dupuytren's disease in a region with 300,000 inhabitants. The indication for treatment with collagenase injections was presence of a palpable cord and a total extension deficit of $\geq 20^{\circ}$ in the MCP joint and/or PIP joint. All patients who had received at least one injection and reached 2 years after first injection from November 2013 through October 2014 were eligible.

Patients

From September 2011 through October 2012, we treated 57 consecutive patients (59 hands) with collagenase injections. In the 2 bilaterally treated patients the interval between treatments was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands) declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50 hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median

25, range 24 to 35) months after first injection (Table 1).

Intervention

- A hand surgeon injected collagenase into the cord using a modification of the standard
- technique.⁴ After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all
- reconstituted collagenase that could be withdrawn (approximately 0.80 mg) in the cord,
- distributed in 3 or 4 spots along the palpable cord, from the PIP joint to the palmar crease.

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After injection, a nurse applied a soft dressing and the hand therapist gave the patient verbal
and written instructions regarding edema prophylaxis and avoidance of heavy use of the hand.

The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal to the collagenase injection sites) to block the nerves to the treated finger. After about a 20minute interval the surgeon performed finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into

- 116 maximum possible extension.
- 117

Immediately after finger manipulation, the patients went to the hand therapist and received a static splint with fingers in maximal possible extension; the therapist gave instructions on edema management, range of motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case contracture correction was incomplete and the patient was willing to receive further treatment, the surgeon scheduled the patient for a second injection.

124

125 Measurements

126 Before treatment, one of three hand therapists measured active extension deficit (AED) in the

- 127 fingers with a goniometer and recorded the results in a standardized protocol. The first 29
- 128 patients in the study completed the 11-item disabilities of the arm, shoulder and hand
- 129 (QuickDASH) scale.⁸ At 5 weeks after injection, a hand therapist measured AED in the
- 130 fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand
- 131 therapist contacted the patients and asked them to attend the hospital for a physical

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132	examination. During this visit, the therapist measured AED as well as passive extension
133	deficit (PED) in the fingers and examined the hand for possible treatment-related
134	complications. The therapist asked the patients to report any symptoms from the treated hand
135	and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients
136	completed the QuickDASH. The same hand therapist (AL) examined all patients who
137	attended the 2-year follow-up evaluation and telephone-interviewed patients who did not
138	attend examination. During the telephone interview, the therapist asked the patients whether
139	they believed their treated finger had worsened since the 5-week follow-up visit and whether
140	they were satisfied with the results. Two of the patients interviewed by telephone also
141	completed the QuickDASH.
142	
143	We reviewed the electronic records of all participants and non-participants to ascertain any
144	subsequent surgery or other procedures on the study hand. We also recorded the number of
145	any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).
146	
147	Statistical analysis
148	Sample size: The primary outcome was treatment effect durability defined as the proportion of
149	patients that do not worsen by $\geq 20^{\circ}$ in AED, in a treated joint, between the 5-week and the 2-
150	year measurements. We considered this cut-off as clinically important because it has been
151	used in the previous collagenase multicenter study. ⁶ In that study, recurrence or nondurability
152	(≥20° increase in PED in fully or partially corrected joints with presence of palpable cord, or
153	subsequent treatment) among 924 joints was 24% at 2 years. We estimated that approximately
154	50 patients would be eligible and a 70% participation rate. With 80% power and 5%
155	significance level, a sample of 30 patients can show treatment effect durability among 75% of
156	the patients.

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157	Primary analysis: We recorded AED values for MCP and PIP joints for all treated fingers at 3
158	measurement times (baseline, 5 weeks and 2 years) and calculated the proportion of fingers
159	that showed worsening of $\geq 20^{\circ}$ in AED from the 5-week to the 2-year measurements.
160	Secondary analyses: In addition to AED values for all MCP and PIP joints and total
161	(MCP+PIP) extension deficit in the treated fingers we analyzed AED values for joints that
162	had at least 10° pretreatment AED. We considered hyperextension as 0° extension deficit.
163	Because previous studies defined complete correction as PED value 0° to 5°, ^{1,6} we also
164	analyzed the data according to this definition. This was possible only for the 2-year values,
165	because we measured only AED at baseline and 5 weeks. The change in AED between
166	evaluation times (baseline, 5 weeks and 2 years) was statistically tested with the paired t-test.
167	We used the Mann-Whitney test to compare baseline and 5-week AED in joints that showed
168	\geq 20° AED worsening between the 5-week and 2-year measurements and joints that had not
169	worsened (only hands that received a single injection were included in this analysis). We
170	tested the change in QuickDASH scores with the Wilcoxon test (one score for both hands for
171	the 2 bilaterally treated patients). We analyzed the correlation between the changes (baseline
172	to 2 years) in total AED and QuickDASH scores with the Pearson correlation coefficient (r).
173	We also analyzed treatment satisfaction according to changes in total AED and QuickDASH
174	scores using analysis of covariance adjusting for sex, age and baseline total AED or
175	QuickDASH score, respectively. We did a similar analysis for the 2-year QuickDASH scores
176	adjusting for sex and age.
177	
178	We present the data as proportions, means with standard deviations or 95% confidence
179	intervals, and/or medians with 25 th and 75 th percentiles as appropriate. For one patient who
180	had surgery on the treated finger 23 months after injection we used the extension deficit
181	recorded immediately before surgery as the 2-year value in all analyses.

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4 5 6	183	A 2-sided p-value of less than 0.05 indicated statistical significance. We used Stata version
7 8	184	14.0 (Stata Corporation, College Station, TX, USA) for the sample size estimation and IBM
9 10	185	SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA) for the statistical
11 12	186	analyses.
13 14 15 16 17 18 9 20 21 22 32 4 25 6 27 28 29 30 12 23 24 25 6 27 28 29 30 12 23 24 25 6 27 28 29 30 12 33 4 35 36 37 38 9 0 41 24 34 45 6 47 48 9 50 51 52 35 4 55 67 89 60 152 53 45 56 78 90 60 152 53 55 55 55 56 78 90 60 152 53 55 55 55 55 55 50 50 50 50 50 50 50 50		

RESULTS

189 Joint contracture

190 Active extension deficit: Between the 5-week and the 2-year measurements, AED had 191 worsened by $\geq 20^{\circ}$ in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a 192 single injection). For all treated fingers, the mean AED for the MCP joints was 54° before 193 injection, 6° at 5 weeks and 9° at 2 years and the corresponding values for the PIP joints were 194 30°, 13° and 16°, respectively (Table 2). Between the 5-week and 2-year measurement mean 195 total AED had worsened by 6° (p=0.031).

197 Comparison of the baseline and 5-week AED in joints that had worsened by ≥20° AED
198 between the 5-week and the 2-year measurements and those that had not worsened showed

199 significant differences for the PIP but not for the MCP joints (Table 3). Thus, PIP joints with

200 a large pretreatment AED and incomplete initial correction were more likely to worsen

201 between the 5-week and 2-year measurements than PIP joints with less severe contracture and

202 good initial correction, but this was not the case for MCP joints. Analyses including only

203 joints with baseline contracture of at least 10° showed similar results.

A larger proportion of PIP than MCP joints showed either persistent or increased AED (figure 1). Total AED had worsened by $\geq 30^{\circ}$ in 8 of the 50 hands (16%; all had received a single injection). Considering only joints with a pretreatment AED $\geq 10^{\circ}$ (47 MCP joints [mean 57°, SD 19] and 31 PIP joints [mean 48°, SD 21]), mean improvement in AED from baseline was 49° (95% CI 41 to 54, p<0.001) for the MCP joints and 25° (95% CI 17 to 32, p<0.001) for the PIP joints.

212	Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection,
213	PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%).
214	A total PED \geq 30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the
215	MCP joints was 3.2° (SD 9; median 0; 25 th and 75 th percentiles 0, 0) and for the PIP joints
216	was 11° (SD 19; median 0; percentiles 0, 20).
217	
218	Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported
219	worsening of their treated finger after the 5-week follow-up.
220	
221	Activity limitations
222	Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1
223	had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the
224	remaining 27 patients (28 hands) the median score (25 th , 75 th percentiles) at baseline was 11
225	(2, 21), at 5 weeks was 3 (0, 9) and at 2 years was 2 (0, 18). Changes from baseline to 5
226	weeks and to 2 years were statistically significant (p<0.001 and p=0.034, respectively) but not
227	changes from 5 weeks to 2 years (p=0.45). The correlation between baseline to 2 years
228	changes in total AED and QuickDASH score was moderate (r=0.49, p=0.010). For all 49
229	patients who completed the QuickDASH at 2 years, the median score was 3 (0, 18).
230	
231	Patient satisfaction
232	The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4
233	hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in
234	total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among
235	"dissatisfied" patients was 39 (SD 36); adjusted mean difference 37 (95% CI 26 to 49,
236	p<0.001). Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for

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- 238 Mean 2-year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied"
- 239 patients 26 (SD 13); adjusted mean difference -16 (95% CI -27 to -5, p=0.007).

- 241 Subsequent surgery and adverse events
- 242 One patient had recurrent MCP contracture after 1 injection and chose to have limited
- 243 fasciectomy, which was done 23 months after injection. No other patients had surgery or
- 244 needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not
- 245 observe and the patients did not report any treatment-related adverse events.

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DISCUSSION

This prospective cohort study of patients with Dupuytren's disease treated with collagenase injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4 patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients who did not respond also were dissatisfied), possibly because of incomplete initial correction or recurrent contracture in the treated finger. Considering its relative simplicity compared to fasciectomy the results of this the 2-year treatment effect durability assessment support the continued use of collagenase injection as an effective treatment option in patients with Dupuytren's disease. Assuming, hypothetically, that all patients with total PED of $>30^{\circ}$ at 2 years receive a new injection (implying almost a third of all patients would need two injections), treatment costs as estimated in a previous study,² would still be lower than costs of surgery. The comparison involves only direct treatment costs and does not take into consideration costs of possible surgical complications.² Since patients with good results may still experience worsening after 2 years, a new assessment with longer follow-up is necessary. Most patients received a single injection but about 10% of the patients needed a second injection because the initial reduction was inadequate. Similar to previous studies of both collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80% of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints that had worsened after the 5-week follow-up had more severe contracture both before treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints.

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270	This may suggest that in case the first injection fails to achieve adequate correction for PIP
271	joints the surgeon should consider a second injection early. This question needs further study.
272	
273	Comparison with other collagenase studies
274	We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2
275	years to facilitate comparison with previous studies. With regard to joint contracture, passive
276	deficit would be equal or less than active deficit. Thus, our posttreatment AED values are
277	conservative when compared to studies that reported posttreatment PED values.
278	
279	In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study
280	(CORDLESS), 621 of 950 (65%) of the initial study participants could be followed. ⁶ The
281	authors defined "recurrence" as contracture worsening by $\geq 20^{\circ}$ combined with presence of
282	palpable cord or further treatment including injection, in successfully treated joints (0° to 5°
283	extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which
284	treatment had initially failed were excluded. Same definition applied to partially corrected
285	joints (improved by $\geq 20^{\circ}$) was termed "nondurability". At 2 years, recurrence had occurred in
286	20% and nondurability in 33%. At 3 years, contracture "worsening" (defined as \geq 20° increase
287	in contracture in fully or partially corrected joints with or without palpable cord, or
288	subsequent treatment) was 28% for MCP and 58% for PIP; no 2-year data for "worsening"
289	are available. The study reported that for successfully treated MCP joints mean PED at
290	baseline was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20
291	(SD 19), respectively, ⁶ and a substantial number of patients received multiple injections. In
292	our study, mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19),
293	respectively.
294	

295	Because we measured PED only at 2 years, it is not possible to make a direct comparison with
296	the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32
297	hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie
298	"successfully treated" according to CORDLESS definition), 2 had PED $\geq 20^{\circ}$ at 2 years and 1
299	had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS.
300	This is an overestimate because in the CORDLESS study the definition of recurrence required
301	that patients had both contracture worsening and palpable cord, and a large number of
302	different surgeons recorded presence of palpable cord (validity uncertain). Although it is
303	difficult to compare results because of differences in definitions, our results appear to be more
304	favorable. A study of 47 patients with 1 MCP contracture (30°-60°) and no PIP contracture,
305	treated with a single 0.58-mg collagenase injection, reported a 25% 2-year recurrence (>20°
306	contracture). ⁹
307	
308	Comparison with limited fasciectomy and percutaneous needle fasciotomy
309	Although many studies have reported fasciectomy results, ¹⁰ we believe only prospective
310	studies with high follow-up participation can provide good-quality outcomes data. A recent
311	prospective study of 90 patients treated with limited fasciectomy at a university hand surgery
312	center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and
313	for the PIP joints 22 (SD 18). ¹¹ It is unclear whether the authors used 0° for hyperextension
314	(as in our study) or used the actual values, which would underestimate the reported extension
315	deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results
316	compare favorably with the 1-year results after limited fasciectomy. Surgery-related
317	complications reported in the study included nerve injury (4 patients) and complex regional
318	pain syndrome (4 patients) and many patients required extensive therapy. ¹¹ Collagenase

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treatment does not require extensive hand therapy. Almost all patients required only two hand therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).

In a randomized study that defined recurrence after needle fasciotomy as $\geq 30^{\circ}$ worsening in

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the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had
recurrence.¹² Applying the same definition to our study but using total AED, 8 of 50 hands
(16%) would be defined as having recurrence.

The Swedish National Quality Register for Hand Surgery have reported outcome data for patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments between 2010 and 2014.¹³ The mean DASH score in patients treated with collagenase had improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52) and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to 100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was 79%, and after closed fasciotomy (n=73) was 69%.¹³ A Swedish 2-center randomized study of collagenase versus needle fasciotomy found no differences at 1 year, but it included mainly patients with only MCP contractures and the treating surgeons measured the outcomes.¹⁴

We do not use the outcome "recurrence" because of lack of consensus about the definition of recurrence. Treatment with collagenase inherently implies that part of the cord is left intact and therefore it would be impossible to know with acceptable certainty whether a presence of a cord is indicative of recurrence. We believe the degree of joint contracture before and after treatment is a more valid measure of outcome irrespective of whether the cause of the contracture is incomplete correction, disease recurrence/progression, or other cause.

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344	
345	Activity limitations
346	We used the QuickDASH as patient-reported measure of activity limitations and the results
347	show that the scores improved significantly after treatment. The magnitude of improvement
348	differed according to changes in joint contracture and with patient satisfaction. Because the
349	median pretreatment QuickDASH score was relatively low, it may not be appropriate in
350	studies comparing different treatments because it would be difficult to detect important
351	between-group differences. However, in patients with Dupuytren's disease, there are no
352	established thresholds for within-group and between-group differences in QuickDASH score,
353	considered as clinically important. Besides, it is not obvious that the same threshold should
354	apply to complex treatments that include surgery and extensive rehabilitation as to less
355	invasive treatments that are associated with substantially lower risks and burden on patients.
356	
357	The limitations of our study include a single center and a moderate sample size, implying
358	uncertain generalizability. We did not measure passive but only active extension deficit at
359	baseline and at 5 weeks after injection and only the first 29 patients completed the
360	QuickDASH at these follow-up times. Another limitation is lack of 12-month follow-up.
361	Further, patients stated whether they were satisfied or not satisfied with the results at 2 years;
362	a scale with more response options might have yielded different results. Our study has several
363	strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2 years,
364	independent of the treating surgeon, and a validated scale used to measure patient-reported
365	activity limitations. The high participation rate is a major strength with 2-year outcomes data
366	available for 95% of the treated hands of patients still living.

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435 Figure legend



Table 1 Characteristics of the participants and non-participants in the 2-year follow-up physical examination

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38:12	8:1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34 : 16	8:1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5:3:1:0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit [†]		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

*Interval: 4 weeks (1 patient), 2 months (1 patient), 6 months (3 patients), all 5 had MCP and PIP contracture at

baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP

correction).

[†]Median (25th, 75th percentiles) active extension deficit (degrees) of the metacarpophalangeal and proximal

interphalangeal joints of the treated finger. For all treated fingers, the minimum total extension deficit was 30°.

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Table 2 Active extension deficit in the treated fingers immediately before collagenase injection (baseline) and at

458 5 weeks and 2 years after injection.

	Baseline	5 wk	2 yr	Mean difference (95%	CI), p-value	
	n = 50	n = 50	n = 50	Baseline - 2 yr	5 wk - 2 yr	
MCP	54 (23)	6 (12)	9 (16)	45 (38 to 52) <0.001	-3.1 (-7.8 to 1.6)	0.20
PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20) <0.001	-3.3 (-6.7 to 0.1)	0.05
MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68) <0.001	-6.4 (-12 to -0.06)	0.03

460 Values are mean (SD) unless specified otherwise.

461 MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

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Table 3 Baseline and 5-week active extension deficit for the joints

463 that had worsened by $\geq 20^{\circ}$ at the 2-year measurement (compared to the

464 5-week measurement) and the joints that had not worsened between these

465 two measurement times; hands treated with a single collagenase injection.

	Worsened ≥20° after the 5-week postinjection measurement	Not worsened after the 5-week postinjection measurement	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 wk	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 wk	15 (15, 55)	0 (0, 15)	0.004

Values are median $(25^{\text{th}}, 75^{\text{th}} \text{ percentiles})$ active extension deficit.

468 MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

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STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the
	P1,2	abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
	P2,3	and what was found
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P5	Present key elements of study design early in the paper
Setting	5 P5	Describe the setting, locations, and relevant dates, including periods of recruitment,
C		exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
	P5,6	selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of
		selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed
		Case-control study-For matched studies, give matching criteria and the number of
		controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and
	P6,7,9	effect modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement	P6,7	assessment (measurement). Describe comparability of assessment methods if there
		is more than one group
Bias	9 P7,8	Describe any efforts to address potential sources of bias
Study size	10 P7	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
~	P7,8	describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
	P7,8,9	(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(<i>d</i>) Cohort study—It applicable, explain how loss to follow-up was addressed
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
		autiessed
		cross-sectional study—11 applicable, describe analytical methods taking account of sampling strategy
		samping suarcy
Continued on most and		(e) Describe any sensitivity analyses
Continued on next page		

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
	P5 &	eligible, examined for eligibility, confirmed eligible, included in the study, completing
	T1	follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
data	T1	information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) Cohort study—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P9-	Cohort study—Report numbers of outcome events or summary measures over time
	11, T2,	Case-control study-Report numbers in each exposure category, or summary measures
	Fig	of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 <mark>P9-11</mark> ,	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
	T2	their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period
Other analyses	17 P9,10	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity
		analyses
Discussion		
Key results	18 <mark>P11</mark>	Summarise key results with reference to study objectives
Limitations	19 P14	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other information	on	
Funding	22 P 17	Give the source of funding and the role of the funders for the present study and, if
		applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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