Using routinely collected data to estimate postoperative complication rates, temporal trends, and geographical variation in Dupuytren's disease surgical management in England

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A thesis submitted in fulfilment of the requirements for the degree of Master of Science by Research (MRes) in Musculoskeletal Sciences

Trinity Term 2019

Table of contents

List of abbreviations **6**

Acknowledgment **8**

Abstract…… **9**

Chapter 1. Introduction **11**

1.1 Definition: 11
1.2 History and nomenclature: 11
1.3 Anatomy of the palmar fascia: 12
1.4 Epidemiology**:** 14
1.5 Aetiology of DD: 15
1.6 Pathology of DD 16
1.7 Clinical features and diagnosis: 17
1.7.1 Clinical features: 17
1.7.2 Diagnosis: 17
1.7.3 Severity grading: 18
1.7.4 Dupuytren's diathesis: 19
1.8 Differential diagnosis: 19
1.9 Treatment**:** 20
1.9.1 Non-surgical treatment: 20
1.9.2 Surgical treatment: 22
1.10 Functional disability and socioeconomic burden of DD: 24
1.11 Data source: 25
1.12 Scope of the thesis: 26
1.12.1 Aims 26
1.13 Funding: 27

Chapter 2. Systematic review of the non-genetic risk factors associated with the development of Dupuytren's Disease (DD) **28**

2.1 **Abstract** 28
2.2 Introduction 30
2.2.1 Rationale and aims 30
2.3 Methods 30

2.3.1 Search strategy 30
2.3.2 Eligibility criteria 31
2.3.3 Protocol registration 31
2.3.4 Data extraction, risk of bias, and level of evidence assessment 31
2.4 Results 33
2.4.1 Study selection 33
2.4.2 Study characteristics 36
2.4.3 Potential predisposing factors: 37
2.4.4 Potential protective factors 46
2.5 Discussion 47
2.1.1 Summary of evidence 47
2.1.2 Limitations and strengths of the review 49
2.1.3 Future work: 50
2.6 Conclusion 51
2.7 Chapter appendix 52
Chapter 3. Dupuytren's disease (DD) patients' characteristics and surgical treatment pathway 62
3.1 Introduction 62
3.1.1 Aims: 62
3.2 Methods 63
3.2.1 Study design 63
3.2.2 Data extraction and cleaning 63
3.2.3 Data analysis 64
3.3 Results 65
3.3.1 Participants 65
3.3.2 Patients' characteristics 66
3.3.3 Surgical treatment pathway 68
3.4 Discussion 69
3.4.1 Limitations and strengths 71
3.4.2 Future work 72
3.5 Conclusion 73
3.6 Chapter appendix 74
Chapter 4. DD postoperative complications and rate of reoperations 78

4.1 Introduction 78
4.1.1 Aims: 79
4.2 Methods 79
4.2.1 Cumulative incidence of postoperative complications 80
4.2.2 Self-controlled case series (SCCS) 81
4.2.3 Survival analysis (time-to-first reoperation after primary DD surgery) ……84
4.3 Results 84
4.3.1 Local and serious systemic postoperative complications 84
4.3.2 Self-controlled cases series (SCCS) 89
4.3.3 SCCS cohort characteristics 89
4.3.4 Association between DD surgery and each serious systemic adverse event……..... 92
4.3.5 Gender and type of surgery analysis 93
4.3.6 Rate of reoperations following primary DD surgery 95
4.4 Discussion 98
4.4.1 Local and serious systemic postoperative complications 98
4.4.2 Self-controlled case series (SCCS) design 100
4.4.3 Rate of reoperations after primary DD surgery 101
4.4.4 Limitations and strengths 102
4.4.5 Future work 104
4.5 Conclusion 104
4.6 Chapter appendix 105
Chapter 5. Temporal trends and geographical variation in the rate of primary Dupuytren's disease (DD) surgery in England 107
5.1 Introduction 107
5.2 Methods 108
5.2.1 Data analysis 108
5.3 Results 110
5.3.1 Temporal trends 110
5.3.2 Geographical variation 115
5.4 Discussion 123
5.4.1 Temporal trends 123
5.4.2 Geographical variation 124

5.4.3 Comparison with the literature 125
5.4.4 Limitations and strengths 126
5.5 Conclusion 127
5.6 Chapter appendix 128
Chapter 6. Summary, conclusions and future perspective 129

Appendix…… 135

References…….. 138

List of abbreviations

A and E	Accident and Emergency Department
AED	Anti-epileptic Drug
AKI	Acute Kidney Injury
BMI	Body Mass Index
BSSH	British Society for Surgery of the Hand
CCG	Clinical Commissioning Group
CCH	Collagenase Clostridium Histolyticum
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DASH	Disabilities of the Arm, Shoulder and Hand
DD	Dupuytren's Disease
DF	Dermofasciectomy
DIPJ	Distal Interphalangeal Joint
EGF	Epidermal Growth Factor
EPHPP	The Effective Public Health Practice Project Quality Assessment Tool
FCE	Finished Consultant Episode
FDA	US Food and Drug Administration
HES APC	Hospital Episode Statistics Admitted Patient Care Database
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases, 10th Edition
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LF	Limited Fasciectomy
LRTI	Lower Respiratory Tract Infection
LSOA	Lower-layer Super Output Area
MCPJ	Metacarpophalangeal Joint
MI	Myocardial Infarction

NDORMS	Nuffield Department of Orthopaedic, Rheumatology and Musculoskeletal Sciences
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
OCEBM	Oxford Centre for Evidence Based Medicine
OCIS	Oxford Centre for Islamic Studies
ONS	Office for National Statistics
OPCS-4	Office of Population Census and Survey, 4th Edition
PCT	Primary Care Trust
PDGF	Platelet-derived Growth Factor
PE	Pulmonary Embolism
PECOS	Population, Exposure, Comparison, Outcomes and Study Design
PIPJ	Proximal Interphalangeal Joint
PNF	Percutaneous Needle Fasciotomy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	The International Prospective Register of Systematic Reviews
QGIS	Geographical Information System Software
RCT	Randomised Clinical Trial
RoB	Risk of Bias
SCCS	Self-Controlled Case Series Study Design
SSI	Surgical Site Infection
TB	Tuberculosis
TGF-β	Transforming Growth Factor Beta
TNF	Tumour Necrosis Factor
WD	Wound Dehiscence

Acknowledgment

First and foremost, I praise my God the Almighty for providing me the opportunity to study at Oxford and conduct this research to help clinicians and patients with hand conditions such as Dupuytren's disease. I am eternally grateful to my family in Palestine (my parents: Hasan and Itaf, my fiancé: Hiba and my siblings: Ayman, Hani, Deema, Mohammed, Sohaib, Moath and Ayham) for being in my life and for their unwavering support. My sincere thanks to my supervisors Prof Dominic Furniss and Prof Daniel Prieto-Alhambra and everyone at NDORMS and Green Templeton College for their insightful guidance and mentorship. I declare that each piece of work described herein was conducted by myself except in the following Chapters:

Chapter 2: Ms Rachel Kuo was a second reviewer in the systematic review and Ms Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford helped in designing and carrying out the search strategy.
Chapter 3: Mr Richard Craig helped in extracting the APC data from the HES dataset and provided support and advice in data cleaning and analysis.
Chapter 4: Dr Albert Prats-Uribe helped in the analysis of Dupuytren's disease postoperative complications and Dr Danielle Robinson helped in the analysis of the self-controlled case series method.
Chapter 5: Mr Simon Abram and Ms Jenny Lane helped in the temporal trend and geographical variation analysis.

Abstract

Introduction: Dupuytren's disease (DD) is a common fibro-proliferative condition of the hand and it is usually treated surgically. The primary aim of this thesis was to evaluate DD surgical management in terms of patient characteristics, risk of postoperative complications and reoperation, temporal trend and geographical variation in England. Secondary aim was to investigate the association between DD and non-genetic factors. Methods: A longitudinal population-based cohort study was conducted using Hospital Episode Statistics database. Cumulative incidence and self-controlled case series methods were used to investigate postoperative complications. Directly standardised rates were calculated to evaluate temporal trends and geographical variation of primary Dupuytren's disease surgery. To investigate the association between DD and non-genetic factors a systematic review was undertaken. Results: Between 1 April 2007 and 31st March 2017, 158,119 DD operative procedures were performed in 121,488 adult patients in England. DD surgery was most commonly performed in male, elderly, white patients living in less financially deprived areas and few comorbidities. Most operations performed were primary limited fasciectomy (LF). There was a significant incidence of local and serious systemic complications following DD surgery. The rate of reoperation was highest after primary percutaneous needle fasciotomy compared to primary LF or dermofasciectomy. There was an overall increasing trend and striking variation in the rates of primary DD surgery in England. A strong association was found between DD and advanced age, male gender, family history of DD, diabetes, heavy alcohol drinking, cigarette smoking and manual work exposure. Conclusions: The study

findings have significant clinical importance as they helps to better understand DD surgical management.

Chapter 1. Introduction

1.1 Definition:

Dupuytren's disease (DD) is also known as Dupuytren's contracture, palmar fascia fibromatosis or benign neoplastic fibromatosis[1]. It is defined as a fibro-proliferative connective tissue disease that results in thickening and shortening of the palmar fascia and flexion deformity of fingers[2] (Figure 1). Although it is a benign condition, it has a progressive course that can be disabling to some patients[3].



Figure 1: A picture of Dupuytren's disease causing flexion deformity of the ring finger. Image from J. S. Dupuytren's contracture overview, *https://www.schreibermd.com/dupuytren* (accessed 21 June 2019)

1.2 History and nomenclature:

The eponym of DD came after the renowned French surgeon, Baron Guillaume Dupuytren, described the condition in his lecture in 1831[4]. Dupuytren was not the first to describe the condition, and in fact many other physicians had studied DD

before this date. The first description of DD is usually ascribed to the Swiss physician Felix Plater who in 1614 provided the first written description of DD; he noted a contracture of the ring and little fingers in a stonemason and documented his finding in his book[5]. In 1777, the English surgeon Henry Cline was the first to dissect cadaveric hands with DD, to specifically describe the involvement of palmar fascia and to propose fasciotomy as a surgical treatment of DD[6]. Sir Astley Cooper, another English surgeon, published a description of the nature and treatment of DD in his book in 1822, 10 years before Baron Dupuytren[7]. He wrote: “The fingers were sometimes contracted by chronic inflammation of the thecae (flexor tendon sheath) and aponeurosis of the palm of the hand … When the thecae is contracted nothing should be attempted for the patient’s relief, no operation or other means will succeed; but when one aponeurosis is the cause of the contraction, and the contracted band is narrow it may with advantage be divided by a pointed bistory, introduced through a very small wound in the integument”[7,8].

Cases resembling DD were described as early as the 12th and the 13th centuries in Icelandic sagas; four cases of putative DD were identified as "miracle cures" as they were treated by priest in Orkney and Iceland[9]. DD is traditionally believed that it originated in the Vikings and their descendants who lived mostly in Northern Europe, hence the condition is sometimes called Viking disease[10,11].

1.3 Anatomy of the palmar fascia:

The key to understanding the pathophysiology of DD and its surgical treatment is a good knowledge of the normal hand anatomy. In the normal hand, a thick fibrous sheet, called the palmar fascia (aponeurosis) complex is located deep to

the dermis and it invests the flexor tendons and small muscles of the hand[12]. The palmar fascia runs from the wrist and crosses over the superficial palmar ligament. It then gives longitudinal extensions to each digit in the form of pre-tendinous bands, spiral bands and lateral digital sheets[13]. DD causes fibrosis and distortion of the palmar fascia and results in the formation of fibrous cords, nodules and skin pitting. According to Luck's concept of the pathogenesis of DD, normal longitudinal components of the palmar fascia are called bands, while the diseased tissues are referred to as cords (Figure 3) (16). Skin pitting develops as result of the involvement of the vertical fibres of Grapow that connect the dermis to the underlying palmar fascia[12,15]. These cords can progress to flexion deformity of the digits, palmar cords result in contracture at the metacarpophalangeal joint (MCPJ) while digital cords can lead to proximal interphalangeal joint (PIPJ) contracture[16,17].

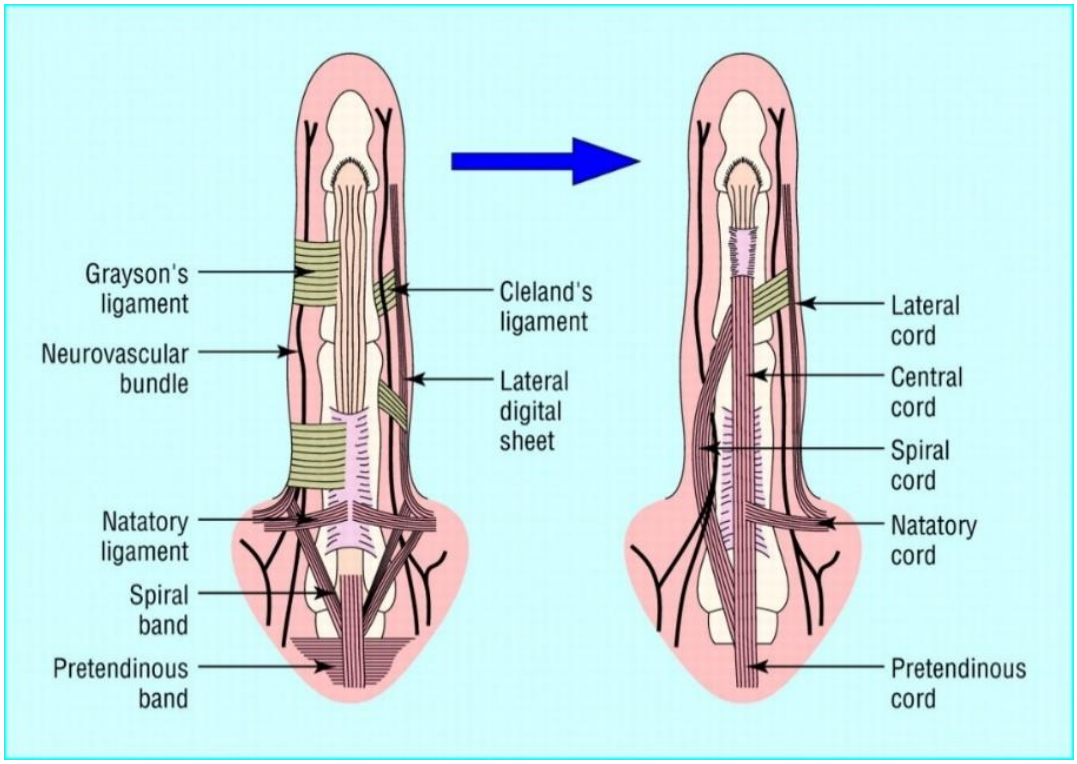


Figure 2: Normal anatomy of the digital fascia (bands) (left) and DD affected fascia (cords) in DD (right). Illustration from Townley WA *et al*. Dupuytren's contracture unfolded. Br Med J. 2006;332(7538):397-400A. Obtained permission to use from Copyright Clearance Center's RightsLink service via BMJ website (order number: 4598720697954)

1.4 Epidemiology**:**

DD is the most common inherited connective tissue disorder and it typically affects northern Europeans and their descendants[3]. Several studies have estimated the prevalence of DD in specific countries and the overall prevalence of DD worldwide ranges from 0.2% to 56%[18]. Ross at al has also described the worldwide prevalence to be from 3% to 42%[19]. The wide variation in the reported prevalence is possibly due to different data collection methods and variation in age, gender, ethnicity and geographical location of the studied population. The highest prevalence of DD is reported in most studies in Norway, Iceland, Northern Scotland, and Australia[20]. In the UK, the estimated prevalence of DD is from 0.2 to 30%, with wide geographical variation[21]. In another study, they have

estimated the prevalence of DD in the UK to be 4% in all ages and increasing to around 20% in the elderly aged 65 and above [22]. In the US, the prevalence is estimated from 4 to 6% in most studies[23]. Sporadic cases have been reported in Africa and Asia as well[24–26].

DD usually affects a more elderly population and it is more commonly seen in males than females. The incidence rises sharply after the fourth and fifth decade, with males and females being affected by the same frequency after the eighth decade[17,19]. The peak age of onset of DD in males is from 40 to 59 years, while for females is from 40 to 69 years[27]. Several epidemiological studies have reported overall male-to-female ratio of DD from 3.0:1 to 9.5:1[5,19,28,29]. Males tends to have bilateral and more severe disease and they present on average 10 years earlier [30–33].

1.5 Aetiology of DD:

Despite significant advances in our understanding of DD, the cause of DD remains elusive. DD is a typical complex disease, similar to rheumatoid arthritis and coronary artery disease[34–36]. Complex disease means that a combination of both genetic and non-genetic (environmental) factors are believed to contribute to the pathogenesis and thus the overall phenotypic expression[37]. Unlike traditional Mendelian modes of inheritance, the manifestations of complex diseases such as DD, are controlled by the liability threshold model[38]. In this model, the larger the genetic and environmental exposure in an individual, the more likely they are to tip over the threshold, and therefore display the disease[34].

In addition to male sex, older age, and family history of DD, other risk factors in the literature include diabetes mellitus, smoking, alcohol consumption and

hyperlipidaemia. Controversy exists as to the significance of most environmental risk factors in general, and especially manual work exposure, hand trauma, epilepsy, antiepileptic drugs intake, and HIV. Interestingly, rheumatoid arthritis and higher BMI are thought to be protective from the development of DD[39,40]. In rheumatoid arthritis patients, anti-inflammatory drugs used might have an inhibitory effect on fibroblast function and proliferation[41].

In order to summarise the evidence for the association between DD and non-genetic (environmental) risk factors, I have conducted a systematic review (see Chapter 2)

1.6 Pathology of DD

Three distinct histological phases have been described in the literature namely; proliferative, involution and residual phases[14]. In the proliferative phase, the environmental factors combined with genetic predisposition result in possible microvascular ischemia and fibroblast transformation into myofibroblasts in the palmar fascia[42]. Local mediators including transforming growth factor beta (TGF-β) and other growth factors such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) are believed to mediate the transformation process[43]. Myofibroblasts deposit type III and to a lesser extent type I collagen leading to formation of nodules and a slowly progressive fibrosis of the palmar fascia[12,44]. The proliferative phase of DD has been compared to the process of tumorigenesis and granulation tissue formation in wound healing[45]. Verjee *et al*[46] have found the histological samples from DD-affected individuals contained inflammatory cells that produce pro-inflammatory cytokines, especially tumour necrosis factor (TNF). TNF helps in the differentiation of fibroblasts into

myofibroblasts via the WNT signalling pathway. Therefore, they have postulated that anti-TNF intralesional injections can prevent progression of DD. A clinical trial is currently being conducted by the same group to determine the efficacy of anti-TNF to halt disease progression in early DD[47].

In the involution phase, myofibroblasts become rearranged along the lines of tension of the hand and they continue to produce more type III collagen.

Finally, in the residual phase, nodules regress leaving relatively acellular collagen-rich visible cords causing contracture and deformity.

1.7 Clinical features and diagnosis:

1.7.1 Clinical features:

The cardinal signs of DD are nodules, cords and flexion deformity of the affected fingers. Skin changes such as pitting and dimpling may also present in DD patients. Contracture usually begins in the palm and then progresses distally to involve the fingers[48]. DD commonly affects both hands, and the ring finger followed by the little finger, and lastly the middle finger are the most commonly involved digits; the index and thumb are usually spared[20].

1.7.2 Diagnosis:

Diagnosis is mostly clinical and several criteria and grading systems have been described. Guidelines from the National Institute for Health and Care Excellence (NICE) UK[49] recommend diagnosis of DD if one of the following clinical manifestations develop:

- Skin changes (thickening, pitting or dimpling on the palm)
- Nodules that are fixed to the skin and palmar or digital fascia. They can be tender when they develop but with time they become non-painful

- Cords defined as: longitudinal, linear thickenings in the palm which extend toward the fingers
- Flexion deformity of the fingers at the MCPJ and PIPJ.

Hueston[50] described a quick and simple diagnostic test (Hueston Table Top Test) in which clinicians ask suspected DD patients to lay their palm and fingers flat on a table. The test is considered positive when the hand cannot lie flat on the table.

1.7.3 Severity grading:

Clinical grading has been also proposed to classify DD according to its severity and to guide surgical management. The most commonly used clinically is described by Tubiana[51]. Tubiana staging system (Table 1) is made up of 5 stages of increasing contracture severity. The staging is based on measurement of the angle made by flexion contracture of the fingers. In each finger, the total flexion deformity is measured at the MCPJ, PIPJ and the distal interphalangeal joint (DIPJ) when involved.

Table 1: Tubiana severity staging of DD – adapted from Tubiana *et al* (1968)[51]

- Stage 0: DD lesion but without contracture
- Stage 1: Flexion deformity between 0 and 45 degrees
- Stage 2: Flexion deformity between 45 and 90 degrees
- Stage 3: Flexion deformity between 90 and 135 degrees
- Stage 4: Flexion deformity more than 135 degrees

As shown in this grading system, contracture doesn't always exist in DD patients and it's not necessary for DD diagnosis. Therefore, many authors prefer the term 'Dupuytren's disease' over the commonly used term 'Dupuytren's contracture'[20].

Another grading used by the British Society for Surgery of the Hand (BSSH) classify DD as mild, moderate or severe[52]. Firstly, mild disease is characterised by no functional disability or contracture. Secondly, moderate disease is characterised by notable functional problems and/or minor contracture. Finally, severe disease is described when major contracture and functional disability exists.

1.7.4 Dupuytren's diathesis:

Dupuytren's diathesis is a term relating to certain clinical features of DD that indicate a more aggressive and recurrent disease. Initially, DD diathesis was described by Hueston[53] and included four features, namely: family history, ethnicity, bilateral disease and ectopic lesions. Hindocha *et al*[54] evaluated and modified Heuston's original description and added two additional factors: male gender and younger onset of the disease (less than 50 year-old). They showed that patients with all six DD diathesis factors have increased risk of recurrent DD after treatment (71% in comparison with 23% in those without any factors).
DD is associated with other tissue-specific fibrotic conditions including knuckle pads in the dorsum of the hand (Garrod’s pads), penile fibrosis (Peyronie’s disease), plantar fibromatosis (Ledderhose's disease) and other organ fibroses[10].

1.8 Differential diagnosis:

Although diagnosis of DD is usually straightforward, other similar conditions[13,55] can be confused with DD including stenosing tenosynovitis (trigger finger), palmar fasciitis and contracture due to diabetic cheiroarthropathy (limited joint mobility) or severe hand osteoarthritis. Other conditions such as soft tissue

tumours of the hand, ganglion cyst and ulnar nerve palsy (claw hand) can also mimic DD.

1.9 Treatment:

Various non-surgical and surgical treatment options have been described for management of DD. Although many non-surgical treatment modalities have been introduced in the last few years, the mainstay of treatment is still surgery[56].

1.9.1 Non-surgical treatment:

Most non-surgical treatment described in the literature lack enough evidence and many are now considered historical. The current non-operative treatments are used as an adjunct to surgery and not meant to replace it. Some of the non-operative options are summarised below:

- **Observation:** Treatment of DD is sometimes not needed and therefore observation can be appropriate for DD patients with non-progressive, painless disease with minimal contracture and no functional disability[57].
- **Physiotherapy:** Physical therapy has variable outcomes in the literature. Ball *et al*[58] have shown in a small pilot study that external overnight splinting reduces digital contracture in DD patient with early disease. Similarly, passive stretching, application of heat and therapeutic ultrasound may be helpful in the early stages of DD[13]. Splinting after DD surgery can help maintain postoperative extension, although the evidence is weak[59]. In a multicentre RCT[60], night splinting after LF or DF showed no statistically significant self-reported benefits compared to physiotherapy alone after 1 year follow-up ($p = 0.703$). Self-reported benefits were

defined as patient satisfaction and hand disability using the Disabilities of the Arm, Shoulder and Hand (DASH) tool.

- **Radiotherapy:** Radiotherapy is thought to halt disease progression via inhibition of myofibroblasts[61]. However, a systematic review looked at the evidence for its use and showed that the evidence for its clinical effectiveness is scarce, and more research is needed. Therefore radiotherapy is considered an unproved method to treat DD[62].
- **Steroid injection:** One study has reported that triamcinolone acetonide intralesional injection can produce 'softening' and 'flattening' of nodules of DD with early disease[63]. Zachariae *et al*[64] used hydrocortisone acetate intralesional injection to treat early DD cases and all patients reported softening of their lesion and resolution of their baseline pain. Ball *et al*[64] conducted a systematic review on the use of steroid in DD patients with early stages. They concluded that intralesional steroid appears to be of benefit but the methodology that the included studies used is weak as the outcome was assessed subjectively. They have also showed that there is no clinical benefit of the use of either oral or topical steroid in DD treatment.
- **Collagenase:** Collagenase Clostridium Histolyticum (CCH) is a novel treatment first approved by the US Food and Drug Administration (FDA) (Xiaflex) in 2010[65]. It was also approved by the European Medicines Agency (Xiapex) in 2011[66]. It is more popular and surgeons have more experience in using it in America, Canada and Australia compared to Europe[67]. CCH is derived from the bacteria *Clostridium Histolyticum* and works by hydrolysing collagen fibres in DD cords and thus allowing the

cords to be severed, relieving contracture[68]. It is mainly indicated for treatment of DD adult patients who have contracture with a palpable cord and have enough skin coverage[65,69]. A double-blind, placebo-controlled, randomised clinical trial (CORD II) was conducted by Gilpin *et al*[70] on 66 DD adult patients who received CCH treatment. They have administered up to three CCH injections into 45 cords (20 MCPJ and 25 PIPJ) in the treatment group and 21 cords in the placebo group (11 MCPJ and 10 PIPJ). The overall success rate (defined as correction to 0 to 5 degrees of full extension a month following the last CCH injection) was 44.4 % compared to 4.8% in the placebo group. There are ongoing randomised clinical trials comparing CCH injection with percutaneous needle fasciotomy, and limited fasciectomy for the treatment of DD in terms of the efficacy, safety and cost-effectiveness[71].

- **Other non-surgical treatments:** Anti-TNF[47], vitamin E[72], Tamoxifen[73], 5-Fluoruracil[74], hyperbaric oxygen therapy[75] have been proposed and some of them have been clinically used in DD patients but their efficacy is uncertain, unproven or short lasting.

1.9.2 Surgical treatment:

Indication for surgical treatment is advanced DD with MCPJ contracture of at least 30 degrees or any degree of PIPJ contracture[76]. The most commonly described surgical options for treatment of DD includes percutaneous needle fasciotomy (PNF) and open surgical procedures such as limited fasciectomy (LF) and dermofasciectomy (DF). Overall, the most popular surgical procedure is open fasciectomy[77].

- **Percutaneous needle fasciotomy (PNF):** PNF, also called needle aponeurotomy, is the least invasive DD surgical procedure that can be done in an outpatient setting. It involves inserting a hypodermic needle or a blade to mechanically divide DD cords under local anaesthesia[78]. It has a quick recovery and can be cost-effective compared to fasciectomy and CCH[79]. The main disadvantages of PNF is its high recurrence rate. In a 5-year follow-up RCT, Rijssen *et al*[80] have found a statistically significant higher recurrence rate of DD following PNF (85%) compared to LF (21%). The same study has suggested PNF as a preferred alternative to LF in elderly patients who prefer quick and less invasive procedures with minimal complications regardless of its recurrence rate. Most surgeons prefer PNF to treat MCPJ contracture as compared with PIPJ. This is because of the higher risk of neurovascular and tendon injury and lower success rate in treating PIPJ[81].

- **Limited fasciectomy(LF):** LF is the most commonly performed surgical technique to treat DD[82]. It involves excision of only the diseased fascia (cords) that cause the contracture. LF is performed under regional or general anaesthesia as day-case surgery with an average of 4 to 6 weeks of recovery[83]. Segmental fasciectomy (aponeurectomy) is a similar but less popular procedure that has been also described to treat DD. In this procedure, short segment(s) of DD cord are removed instead of the whole cord as in LF[84]. It has a shorter recovery period (2 to 3 weeks) but a higher recurrence rate (38%)[81,85].

- **Dermofasciectomy(DF):** DF is the most invasive approach in which the diseased fascia and the overlying skin are surgically removed[56]. Skin coverage is done using skin graft or less commonly cross finger flap[86]. DF is mainly indicated for recurrent DD, young patients with strong DD diathesis, and for patients with grossly visible skin involvement[87,88]. Although DF may reduce recurrence, it has some disadvantages including longer recovery, and graft or flap failure[81].

1.10 Functional disability and socioeconomic burden of DD:

Studies[89,90] have found that as DD contracture deformity increases, hand function becomes worse. They have also found that DD surgery improved hand function as measured by Sollerman test compared with their preoperative baseline. The degree of improvement of hand function after surgery was more significant with earlier surgical intervention[91]. In a study by Engstrand *et al*[92], most of DD patients reported activity limitations in self-care (42%), followed by 33% reporting disability affecting their work. 25% reported problems in spending their leisure time. Surgery improved their hand function and their overall performance.

Bebbington *et al*[93] have found the number of DD diagnoses and its surgical procedures have been increasing over the last few years especially in the elderly population. They expect that the figures will continue in the same trend in the future. For instance, 16,797 DD surgical procedures were performed in England in 2015 and the number is expected to increase to 25,242 DD operations in 2030. More detailed temporal trend analysis of DD surgical treatment in England can be found in Chapter 5.

Costs for DD surgical procedures in England in financial year 2010-2011 were £41,576,141 as estimated by Gerber *et al*[94]. They have also estimated the daily cost per DD patient as £2,885 for day case procedure and £3,534 for admitted patients. The high cost of DD surgery requires more comprehensive cost-effectiveness studies to evaluate various DD treatments that are needed to meet the increasing demand.

1.11 Data source:

I have analysed a prospectively collected Admitted Patient Care (APC) data from the Hospital Episode Statistics (HES) dataset. HES is a database that contains information about all patient hospital episodes including admissions, accident and emergency (A and E) department attendances and outpatient appointments at all National Health Services (NHS) hospitals in England. HES data also includes details of NHS England hospital episodes presented at healthcare centres (including in the independent sector) funded by the NHS, private patients treated in NHS hospitals, and patients who are residing outside England but treated at NHS hospitals in England[95]. Each episode recorded in HES represents a 'Finished Consultant Episode (FCE)' which means a 'continuous period of care under one consultant[96]. In HES dataset, diagnoses are recorded using the International Classification of Diseases, 10th revision (ICD-10) classification system in 24 fields. Surgical procedures are documented using the 4th edition of the Office of Population Census and Survey (OPCS-4) codes in 20 fields.

My Upper Limb Epidemiology group obtained a HES dataset extract from NHS Digital (application reference number: DARS-NIC-29827-Q8Z7Q). The University of Oxford Research Support Services (reference number: 12787) and the 'NHS

Data Access Advisory Group' have approved the study. The research project was registered at ClinicalTrials.gov (identifier: NCT03573765)[97] as an observational study. As per the ONS ethical regulations, I have passed the Safe Researcher Training and obtained an ONS Accredited Researcher number (ONS20972) before accessing the data. I have also complied with my Departmental (NDORMS) Information Governance guidelines. For the purpose of this study, mortality data from the Office for National Statistics (ONS) has been linked with my HES data extract.

1.12 Scope of the thesis:

This thesis is titled “Using routinely collected data to estimate postoperative complication rates, temporal trends, and geographical variation in Dupuytren's disease surgical management in England”. So, as part of my thesis, I have analysed HES data trying to answer certain epidemiologic questions regarding surgical treatment of DD. In addition, as there is conflicting evidence regarding the non-genetic risk factors that predispose to DD, I have synthesised the evidence using a systematic review.

1.12.1 Aims

The following chapters have these broad aims:

1. Systematic review looking at the evidence for the non-genetic (environmental) risk factors associated with the development of DD (Chapter 2).
2. To report patient characteristics (age, gender, ethnicity, Charlson comorbidity index, and index of multiple deprivation (IMD) deciles) of those who had surgical operations of DD in England. Moreover, to describe the

surgical treatment pathway of the DD surgical operations followed in the study period. (Chapter 3).

3. To estimate the rate of postoperative local and serious systemic complications following DD surgery and to know the risk of reoperation following primary DD surgery (Chapter 4).
4. To estimate temporal trends and geographical variation in primary DD surgery in England (Chapter 5).
5. Summary, conclusions and future perspective of the thesis (Chapter 6).

1.13 Funding:

The author is fully funded by the Oxford Centre for Islamic Studies (OCIS) Scholarship. The funding body has no influence on the study in any of its stages.

Chapter 2. Systematic review of the non-genetic risk factors associated with the development of Dupuytren's Disease (DD)

2.1 Abstract

Introduction: Dupuytren's disease (DD) is a common complex disease where multiple genetic and non-genetic factors contribute in its etiology. The role of the non-genetic risk factors is still unclear and there are conflicting studies in the literature. This review aimed to synthesise the evidence regarding the association between non-genetic factors and DD.

Methods: A search strategy was developed based on the PECOS[a] analysis framework. Following PRISMA guidelines, a literature search was conducted using Ovid Medline, Ovid Embase, Scopus, Web of Science, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials databases from their inception to November 2018. Title and abstract, and then full-text screening against predefined eligibility criteria was performed independently by two reviewers and consensus was achieved by a third reviewer. The EPHPP and the OCEBM[b] tools were used to assess study quality and to evaluate the level of evidence of included studies respectively. This review was registered on PROSPERO (CRD42019121487).

Results: Reviewers identified 4434 studies, of which 54 were included in the qualitative analysis. There was a strong evidence for the association between DD and advanced age, male gender, family history of DD and diabetes mellitus. Furthermore, heavy alcohol drinking, cigarette smoking and manual work

[a] **PECOS:** Population, Exposure, Comparison, Outcomes and Study
[b] **OCEBM:** Oxford Centre for Evidence Based Medicine

exposure showed a significant dose-response relationship. The quality of the studies was mostly low or moderate and most studies were level 4 or 3 on the OCEBM levels of evidence.

Conclusions: The study results show a strong association between DD and advanced age, male gender, family history of DD, DM, heavy alcohol drinking, cigarette smoking and manual work exposure. Further robust studies are needed to explain the causal relationship of these associations.

2.2 Introduction

2.2.1 Rationale and aims

As discussed in Chapter 1, DD is a complex disease of the palmar fascia where various genetic and non-genetic risk factors play a role in its pathogenesis.[34–36] The role of various non-genetic factors remains controversial. Several narrative reviews[12,17,20,30,48,98,99] in the literature assess some proposed associations with DD but very few systematic reviews have been performed. Broekstra *et al* [100] conducted a systematic review to evaluate the association between DD and diabetes mellitus, liver disease and epilepsy only. Descatha *et al*[101] undertook a systematic review investigating the association between DD and work exposure. No systematic review in the English literature investigated the role of other non-genetic factors such as age, gender, family history of DD, smoking, previous hand trauma, hyperlipidaemia, rheumatoid arthritis and other proposed factors. In view of the controversy and lack of comprehensive systematic review of the association between DD and non-genetic factors, this systematic review was undertaken.

2.3 Methods

2.3.1 Search strategy

Search questions and strategy were developed based on the Population, Exposure, Comparison, Outcomes and Study design (PECOS) analysis framework. The PECOS literature search was conducted on 26-27 November 2018 as described in table 1 in the Appendix. The following databases were used to search the literature: Ovid Medline (1946 to November 2018), Ovid Embase (1974 to November 2018), Scopus, Web of Science Core Collection, Cochrane

Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (Issue 11 of 12, November 2018).

2.3.2 Eligibility criteria

Two reviewers (OA and RK)[c] screened title, abstract and finally full-text articles against the following inclusion and exclusion criteria (Table 1):

Table 1: Inclusion and exclusion criteria for abstract and full text screening

Inclusion criteria:
Observational studies: (Case-control studies, cross-sectional studies and cohort studies)
Exclusion Criteria:
1. No comparator (control) group 2. Publication not written in English language 3. Case reports, case series, conference abstracts and letters to editor 4. Animal studies, cell studies and cadaver studies

2.3.3 Protocol registration

The study protocol was registered in the PROSPERO international prospective register of systematic reviews (CRD42019121487)[102].

2.3.4 Data extraction, risk of bias, and level of evidence assessment

This review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[103] to report the systematic review as described in the flowchart (see section 2.4.1). A comprehensive data extraction

[c] Reviewers are: Osaid Alser (OA) (1st and author of this thesis), Rachel Kuo (RK) (2nd) and Dominic Furniss (DF) (3rd and main supervisor)

spreadsheet was produced using Microsoft Excel (2016) and included information about country where the study was conducted, study design and patients' demographics (number of patients, age, gender, ethnicity and occupation). Other information included conflict of interest statement, funding, ethical approval, statistical analysis used, risk factors studied and how they were defined. The final section included results, limitations and strengths of the study, and key conclusions. The Effective Public Health Practice Project (EPHPP)[104] quality assessment tool for quantitative studies was used to assess the quality and risk of bias of the included studies. EPHPP classifications was as follows; strong (1), moderate (2) and weak (3). The Oxford Centre for Evidence Based Medicine (OCEBM) classification[105] (Table 2) was used to provide judgement about the level of evidence of the included studies. Two reviewers (OA and RK) extracted the data, assessed the quality of the studies and summarised the level of evidence for each study independently. Where the two reviewers encountered a conflict, consensus was achieved with the help of the third reviewer (DF). Descriptive analysis of patients' demographics was used. Endnote v9 was used for data management and removal of duplicate articles. Meta-analysis was not conducted as the studies were not homogenous and because of the high risk of bias in significant numbers of the studies.

Table 2: Oxford Centre for Evidence Based Medicine (OCEBM) levels of evidence*

OCEBM level of evidence	Meaning
Level 1	Systematic review of cross sectional studies with consistently applied reference standard and blinding
Level 2	Individual cross sectional studies with consistently applied reference standard and blinding
Level 3	Non-consecutive studies, or studies without consistently applied reference standards
Level 4	Case-control studies, or "poor or non-independent reference standard"

*Based on the diagnosis section

2.4 Results

2.4.1 Study selection

A total of 4434 relevant citations (Table 3 and figure 1) were identified through database searching. Following electronic removal of duplicates (n=2141), 2293 abstracts were screened independently by the two reviewers (OA and RK) against the eligibility criteria. Further duplicates (n=19) were identified manually and excluded. After excluding 2195 abstracts which did not meet the inclusion criteria, 79 full-text articles were further screened by the same two reviewers. A total of 54 results were finally included in the analysis. The third reviewer (DF) supervised title and abstract and full-text screening and resolved any conflict in inclusion or exclusion during these two stages. After full-text screening, 25 studies were excluded for the following reasons: 16 studies had no control group, 3 studies were not relevant, two further duplicates, two conference abstracts and two full-texts were written in non-English language.

Table 3: Number of results extracted for each used search database

Search Database	Number of articles
Ovid Medline	777
Ovid Embase	1081
Scopus	1597
Web of Science Core Collection	822
The Cochrane Library	159
Total	4434

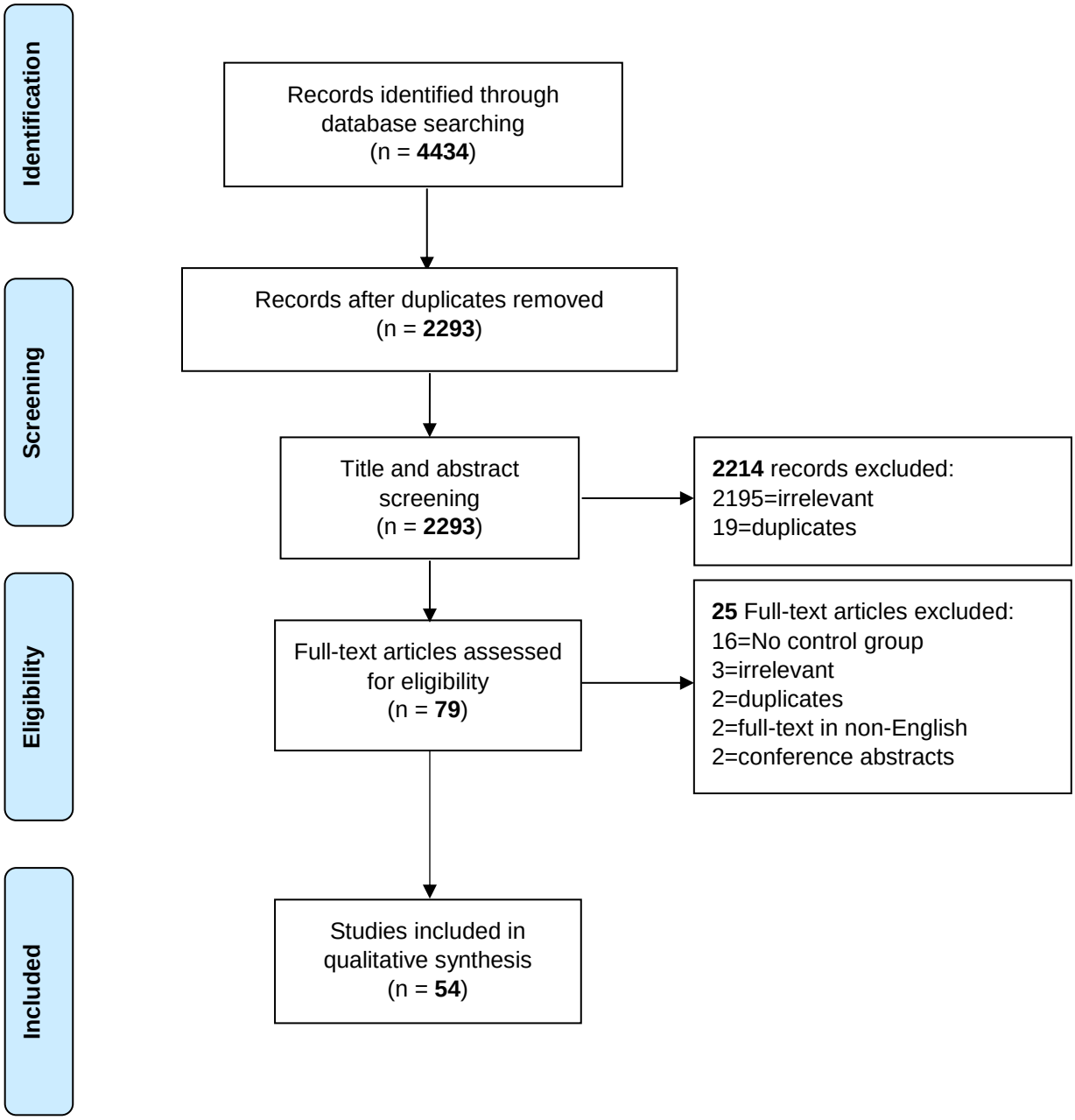


Figure 1: PRISMA flow diagram illustrating the flow of information through different phases of the systematic review

2.4.2 Study characteristics

Most included studies[d] (n=37) evaluated diabetes mellitus as a potential risk factor for DD. Other studies evaluated heavy alcohol drinking (n=15), manual work exposure (n=14), cigarette smoking (n=13), increased age (n=11), male gender (n=8), epilepsy (n=7) and previous hand trauma (n=6). Miscellaneous studies (n<6 per risk factor) included chronic liver disease, family history of DD, hyperlipidaemia, antiepileptic drugs (AED) use, hypertension, ischemia heart disease, HIV, asthma, COPD, gout, algodystrophy, malignancy (unspecified), tuberculosis (TB), haemochromatosis. Finally, a few studies evaluated potential protective factors from the development of DD. These included 3 studies focusing on increased body mass index (BMI) as an indication of obesity and two studies evaluating rheumatoid arthritis.

The majority of included studies had low quality (n=23, (43%)). Sixteen studies (30%) had moderate quality and 15 (28%) had high quality. Most included studies (n=51, (94%)) were graded either OCEBM level 4 (n=41) or level 3 (n=10). Only 3 studies were graded level 2. Twenty-four (44%) studies obtained ethical approval from relevant ethical committees. One study[106] obtained permission from the clinician in charge of the patients but it was not clear if the patients gave consent. Only 5 studies clearly mentioned they did not receive any funding, whereas the remaining 18 studies clearly stated their funding source. The majority of the studies (n=31, 57%) did not indicate their source of funding. More than half of the studies (n=30, 56%) did not include a conflict of interest statement and 24 studies

[d] Not mutually exclusive: Several studies evaluated more than one risk factor per study so the total number of the studies described here doesn't equal to the number of studies included in this review

(44%) declared no conflict of interest. Out of the funded studies, 5[33,107–110] did not mention conflict of interest statement raising concern about possibility of conflict of interest.

DD was diagnosed by qualified doctors in most of the included articles (n=48, 89%). Nurses and medial students trained to diagnose DD based on clinical criteria and pictures of DD in the hand from a medical textbook, diagnosed DD in one article[111]. In 4 studies[112–114], patients self-reported DD by filling in a questionnaire. Finally, the method of DD diagnosis was not clear in one study[115].

All included studies had a comparator (control) group, 30 studies (55.56%) were case-control studies, 15 studies (27.78%) were cross-sectional studies, and 9 studies (16.67%) were cohort studies. One[116] of the cohort studies was a retrospective study. Two thirds of the studies (n=36) were performed in European countries (mostly UK, France, and Nordic countries). The remaining studies were performed in North America (n=7), the Middle East (n=5), East and South Asia (n=4), Africa (n=1) and Australia (n=1). Below is a narrative description of each of the studied risk or protective factor.

2.4.3 Potential predisposing factors:

2.4.3.1 Demographic Characteristics

2.4.3.1.1 Age (Table 1 in the supplementary file – at the end of the thesis)

Out of the 54 included studies, 11 (20%) investigated the association between age and DD. All of these studies[33,111,123,112,116–122] showed a strong evidence for an association between advancing age and DD. The quality of these studies (EPHPP) was mostly strong (n=5) or moderate (n=5), with one weak study (n=1). The level of evidence (OCEBM) was either level 3 (n=5) or level 4 (n=6). Two

studies found an ‘age threshold’ above which the risk of DD development becomes significant. One of these studies[112] showed a threshold of 60 years old while the other study[120] found a lower threshold of 40 years old. The severity of DD, reflected by DD requiring surgery, was also linked to advancing age[112].

2.4.3.1.2 Gender (Table 2 in the supplementary file)

Eight studies (15% of all included studies) evaluated gender in relation to DD. Seven of these eight[33,111,117,120–123] found a significant association between male gender and DD. One[33] of these studies reached the same conclusion but did not report exact numbers or perform statistical analysis. The quality of the studies (EPHPP) that confirmed the association was mostly strong (n=4) or moderate (n=3). The level of evidence (OCEBM) was either level 3 (n=4) or level 4 (n=3).The remaining study[119] (weak quality, level 4 OCEBM) showed no difference between male and female genders but again without any statistical analysis.

2.4.3.1.3 Family history of DD (Table 3 in the supplementary file)

Four studies[110,121,122,124](7%) investigated family history of DD; 3 of these studies[110,121,122] showed a significant association between family history DD and DD. The quality of these three studies (EPHPP) was variable (strong (n=1) or moderate (n=1), weak (n=1)). The level of evidence (OCEBM) was either level 3 (n=2) or level 4 (n=1).The remaining study[124] (moderate quality, level 4 OCEBM) found no association likely due to a very small number of DD patients in the case (n=5 cases) and control groups (n=2 cases).

2.4.3.2 Medical conditions

2.4.3.2.1 Diabetes (Table 4 in the supplementary file)

Out of the 54 included studies, 37 articles[33,106,119–121,123–129,108,130–139,109,140–146,110,112,114–117] evaluated diabetes mellitus (DM) as a potential risk factor for DD. DM was strongly associated with DD in most of these studies[112,114,129–131,133,135,140–144,115,145,146,116,117,120,123,125–127](n=24/37, 65%). Their quality (EPHPP) was variable as follows; weak (n=9), moderate (n=8) and strong (n=7). Their level of evidence (OCEBM) was mainly level 4 (n=19), while some studies were level 3 (n=4) and one study was level 2.

Several studies found that patients who had suffered from DM for a longer duration were more likely to develop DD[114,127,128,131,134,140,141,143]. One of these studies[114] found that longer duration of DM was associated with more severe reported DD symptoms. Three studies[127,128,144] found that DD was more common in patients with type 1 DM than in those with type II DM, however, two other studies[115,142] reported no significant difference between the prevalence of DD in type I and type II DM. A study by Geoghegan *et al*[133] found that patients with insulin-requiring DM, and to a lesser extent DM requiring oral anti-diabetic medications, had increased risk of DD compared to diet-controlled DM. However, Ravid *et al*[143] found no significant difference in DD prevalence between modes of DM treatment. Poor glycaemic control (indicated by high level of HbA1c) was associated with increased risk of DD[120,141]. Microvascular complications of DM such as nephropathy, neuropathy, and retinopathy were also linked with a statistically significant increase in prevalence of DD in two studies[131,141].

The remaining studies (n=13) refuted the association between DM and DD. The quality of these studies (EPHPP) was as follows; weak (n=6), moderate (n=4) and strong (n=3). The level of evidence (OCEBM) was mainly level 4 (n=10),

while some studies were level 3 (n=2) and level 2 (n=1). The lack of association between DM and DD in these studies could be due to small sample size or poor study design or other reasons. For instance, Gebereegziabher *et al*[124] conducted a small study (4/77, 5.2% in the case group, 6/75, 8% in the control group), and it was not clear how they selected control group. Gordon *et al*[119] did not perform formal statistical analysis. Gudmundsson *et al*[33] did not mention the criteria they used to diagnose DM, and their results only reached significance for men. They commented that there were 'not enough women to comment on'. Although they found no association between DD and glucose tolerance test, DM or family history of DM, they found an association between level of fasting blood glucose and DD. Haines *et al*[121] based their DM diagnosis on self-reported information and had a low response rate to their questionnaire especially among control group. Hnanicek *et al*[108] had a small study (90 DD cases and 33 non-DD controls (non-DD)), diagnosed DM based on undefined criteria, did not perform formal statistical analysis, and only a subset of DD patients were included in the analysis (undergoing surgery for DD). Hou *et al*[136] had a small number of DD cases (n=6 per 100,000). Kermani *et al*[138] had also a small sample size (n=1/100 (1%) of cases, 2/100 (2%) of controls) and it was unclear how they recruited or matched controls. Kidwai *at al*[139] had low numbers of DD patients (2/210, 1% of cases, no DD cases in the control group) and they did not perform formal statistical analysis. Larkin *et al*[106] did not adjust for confounders and there was no gender matching in control group. They found a statistically significant association in women between DD and diabetic retinopathy but not with DM. Livingstone *et al* [109] conducted a small study (23 DD cases and 49 controls with no DD diagnosis) with no defined criteria for DM diagnosis. They found no difference between DD

and non-DD patients in terms of levels of fasting blood glucose and fructosamine but they did not perform formal statistical analysis.

2.4.3.2.2 Alcohol use and liver disease

2.4.3.2.2.1 Alcohol use (Table 5 in the supplementary file)

Of the 54 included studies, 15[107,108,124,147–149,110–112,117,118,121–123] examined the association between alcohol consumption and DD. Two thirds (n=10)[108,110–112,117,122,124,147,148] of the studies that evaluated alcohol use as a potential risk factor for DD reported an association. The quality of these studies (EPHPP) was mainly strong (n=5), but some were moderate (n=3) and weak (n=2). Half of these studies was level 3 OCEBM (n=5) and the other half was level 4 OCEBM (n=5).The threshold after which alcohol consumption increases the risk of DD differs between these studies. However, two studies[111,116] found that alcohol consumption increases the risk in a dose-response relationship; meaning that a heavier alcohol consumption was associated with more risk of developing DD. The remaining studies[107,118,121,123,149] (moderate quality (n=4), low quality (n=1), all level 4 OCEBM (n=5)) did not find a relationship between alcohol consumption and DD development. However, one of these study[123] found that alcohol drinking was associated with more aggressive DD, defined by multiple digit disease and involvement of radial rays. It concluded that daily alcohol consumption was predictive of DD progression.

2.4.3.2.2.2 Liver disease (Table 6 in the supplementary file)

Five studies[117,118,148,149] evaluated the link between chronic liver disease and DD. There was no association between chronic liver disease or cirrhosis and DD in four of the five evaluating studies[117,118,148,149]. Their EPHPP quality was low (n=2)

to moderate (n=2) and all had OCEBM level 4 evidence. In these studies, DD was attributed to the effect of alcohol rather than liver disease *per se*. However, one study[148] (moderate EPHPP quality and OCEBM level 4 evidence) did demonstrate an association between cirrhosis and DD. However, the study evaluated patients with DD who had had surgery, and did not adjust for confounders such as alcohol use.

2.4.3.2.3 Epilepsy and anti-epileptic drugs (Table 7 in the supplementary file)

Seven studies[110,119,122,124,130,133,150] examined the association between DD and epilepsy and/or anti-epileptic drugs. Most of these studies (5/7)[29,33,48,53,54] found that the evidence of their role in the aetiology of DD is weak or uncertain. The quality of these studies (EPHPP) was as follows: strong (n=2), weak (n=2) and moderate (n=1). All were level 4 OCEBM except one which was level 3. There were only two studies that showed an association between DD and epilepsy[110,122] (both were of weak EPHPP quality), Lanting *et al*[122] (level 4 OCEBM) showed a borderline association (OR=4.03 (1.01–16.04), p value=0.05) while Lucas *et al*[110] (level 3 OCEBM) found a strong evidence (OR=5.08 (1.63-15.78)) supporting the association of epilepsy with DD in men.

2.4.3.2.4 Hyperlipidaemia (Table 8 in the supplementary file)

Five studies[33,108,109,130,151] evaluated the association between hyperlipidaemia and DD, of which three[33,108,109] found no apparent association between hyperlipidaemia (high serum cholesterol or triglyceride) and DD. These studies had various EPHPP qualities (strong (n=1), moderate (n=1) and weak (n=1)) while two studies were OCEBM level 4 and one was level 3. However, two

studies[130,151] showed a significant association between hyperlipidaemia and DD but not disease progression (severe DD requiring surgery). The EPHPP quality of these two studies was strong (n=1) and weak (n=1) and the OCEBM level of evidence was 4 (n=1) or 3 (n=1).

2.4.3.3 Smoking (Table 9 in the supplementary file)

Thirteen[33,111,132,147,152,112,113,117,121–124,131] of 54 studies evaluated the link between smoking and DD. Eight studies[33,111,117,123,131,132,147,152] showed strong evidence suggesting cigarette smoking as a risk factor for DD. The quality of these studies (EPHPP) was as follows: strong (n=3), weak (n=3) and moderate (n=2). Six studies were level 4 OCEBM and two studies were level 3.Three of these studies[33,111,147] showed that the association follows a dose-response relationship, meaning that people who smoke heavily have greater risk of DD development. Five studies[112,113,121,122,124] showed the evidence for an association is weak or inconclusive, however this could be due to small sample size. For instance, Gebereegziabher *et al*[124] had 77 cases (with DD) in his study and Lanting *et al*[122] evaluated 169 DD cases. The quality of the studies (EPHPP) that refuted the association was as follows: moderate (n=3), weak (n=1) and strong (n=1). Three studies were level 4 OCEBM and two studies were level 3.

2.4.3.4 History of manual work (Table 10 in the supplementary file)

Fourteen studies[33,108,153–156,110,112,113,117,119,121,123,124] examined an association between manual labour and DD. The majority of the studies[33,108,110,112,113,121,123,153–155] (10/14) that evaluated manual work exposure as a risk factor of DD did show an association. The quality of these studies

(EPHPP) was as follows: moderate (n=4) and strong or weak (n=3 each). They were level 3 or 4 OCEBM equally distributed (n=5 each). Most (6/10) of these studies[110,112,113,123,154,155] found the relationship followed a dose-response relationship meaning 'heavy' manual work exposure had a stronger association with DD compared to low or moderate exposure. 'Heavy' manual work definition was inconsistent between the included studies. Manual work involving vibration tools was associated with DD in three[112,113,154] of the studies that confirmed a relationship between manual work exposure and DD. One study[121] found a positive association between repetitive manual work and DD but not heavy or vibration-associated manual work exposure. The remaining studies[117,119,124,156] found no or an inconclusive relationship between manual exposure and DD. The quality of these studies (EPHPP) was as follows: moderate (n=2) and strong or weak (n=1 each). They were mainly level 4 OCEBM (n=3) and one study was level 2.

2.4.3.5 History of previous hand trauma (Table 11 in the supplementary file)

Six studies[108,110,117,121,122,155] examined the association between previous hand trauma (variably defined between these studies) and DD. Five[108,110,117,122,155] showed an association between history of previous hand trauma and DD. One of these studies[108] concluded that there was an association but without showing any relevant results. The quality of the studies (EPHPP) that showed an association was as follows: moderate or weak (n=2 each) and one strong study. They were mainly level 4 OCEBM (n=3) and two studies were level 3. The remaining study[121] (moderate quality, level 4 OCEBM) denied any association between previous hand trauma and DD.

2.4.3.6 Miscellaneous (Table 12 in the supplementary file)

There were several studies (n=15) that evaluated the association of other potential risk factors with DD. The quality of these studies (EPHPP) was as follows: strong (n=6), moderate (n=5) and weak (n=4). They were mainly level 4 OCEBM (n=9) and six studies were level 3. Generally there were between 1 and 3 studies per risk factor, so results may be considered preliminary at best. This inconsistency is illustrated by 3 studies[106,124,130] that investigated the association between hypertension and DD. One study[130] found an evidence for association between hypertension and DD, but not with disease progression requiring surgery. Another study[124] found a higher incidence of DD among patients with hypertension compared to controls but the study was underpowered and this was not statistically significant. The final study[106] showed no evidence for any association between hypertension and DD. Three[119,123,130] other studies evaluated the association between ischemic heart disease and DD. Two of these studies[123,130] found an association between ischemic heart disease and DD, whereas the final study did not[119]. Tuberculosis (TB) was evaluated by two studies; one study[124] found no evidence for any association with DD and the other study[119] concluded that TB may have an association with DD but the evidence was inconclusive. Other conditions such as Ledderhose's disease (plantar fibromatosis)[122], asthma[130], COPD[130], malignancy (unspecified type)[130], gout[130], algodystrophy (complex regional pain syndrome)[109] were found to be significantly associated with DD. Other potential risk factors were not found to be associated with DD (haemochromatosis)[108] or their evidence was inconclusive (HIV)[157].

2.4.4 Potential protective factors (Table 13 in the supplementary file)

2.4.4.1 Body mass index (BMI)

Three studies[33,120,133] evaluated the association between obesity (as reflected by high BMI) and DD. Two of these studies[33,120] (both strong EPHPP quality and level 3 OCEBM) found the risk of DD was inversely proportional to increasing BMI. Gudmundsson *et al*[33] showed that men with DD had lower mean body weight and BMI compared to control group of non-DD patients. Hacquebord *et al*[120] found morbid obesity (defined as BMI of 40 or more) had a 47% lower relative risk of DD compared to normal BMI (18.5-24.9). They also concluded that an increase of 1 unit of BMI was found to decrease the odds of a DD diagnosis by 3%. Another study[133] (strong EPHPP quality and level 4 OCEBM) found no significant association between increasing BMI and risk of DD development.

2.4.4.2 Rheumatoid arthritis

Arafa *et al*[39] found a significantly lower prevalence of DD in the hands of rheumatoid arthritis patients compared to a control group. This EPHPP quality of this study was low and its OCEBM level of evidence was 4. However, Wijnen *et al*[130] found no evidence for association between rheumatoid arthritis and DD development. Its EPHPP quality was strong and the OCEBM level of evidence was 3 which could possibly mean that evidence is in favour of the second study; meaning no association between rheumatoid arthritis and DD.

2.5 Discussion

2.1.1 Summary of evidence

Table 4 shows various associations for DD development described in the included studies. There is a strong evidence for association between DD and several demographic factors, including male gender, advanced age, and family history of DD. The strongest evidence for another medical condition associated with DD is for DM, both type 1 and type 2. Not only is the disease itself associated with DD, but its presence for a longer duration, poor glycemic control and microvascular complications such as nephropathy, neuropathy, and retinopathy regardless of DM type are all associated with DD, across multiple studies with different designs. This adds strength to the conclusion that DM is likely to predispose to DD.

Furthermore, the evidence was also strong for heavy alcohol drinking, cigarette smoking and manual work exposure, including vibration tools. In all cases, a dose response relationship between exposure and DD was demonstrated, again strengthening the case for a causative role of these factors in the predisposition to DD.

The evidence was moderate for history of previous hand trauma and hyperlipidaemia. The evidence for the remaining risk factors is weak or inconclusive; these factors are: chronic liver disease, epilepsy, anti-epileptic drugs, ischemia heart disease, hypertension, Ledderhose's disease (plantar fibromatosis), asthma, COPD, gout, complex regional pain syndrome, malignancy, haemochromatosis or chronic infections such as TB and HIV.

The results have also showed that rheumatoid arthritis and higher BMI may be protective from developing DD but the number of the studies was not enough to draw a definitive conclusion. The evidence is perhaps stronger in the case of

BMI, where two of three studies showed an inverse association of DD with BMI in a total of 2,051,100 individuals, with the remaining study that showed no association having just 2,463 individuals.

Table 4: Summary of Dupuytren's disease (DD) associations*

	Strong evidence	Moderate evidence	Weak or inconclusive evidence
Demographics			
Advanced age	*		
Male gender	*		
Family history of DD	*		
Medical conditions			
Diabetes mellitus	*		
Heavy alcohol drinking	*		
Chronic liver disease			*
Epilepsy and antiepileptic drugs			*
Hyperlipidaemia		*	
Smoking	*		
History of manual work	*		
History of hand trauma		*	
Miscellaneous			
Ischemia heart disease			*
Hypertension			*
Asthma or COPD			*
Gout			*
Algodystrophy (complex regional pain syndrome)			*
Malignancy (unspecified)			*
Haemochromatosis			*
Chronic infections (TB and HIV)			*

Possible protective factors		
High BMI	*	
Rheumatoid arthritis		*

*Based on mainly EPHPP study quality and OCEBM levels of evidence

2.1.2 Limitations and strengths of the review

Meta-analysis was not performed because of the diversity or heterogeneity of the included studies in terms of study design, effect size measures and adjustment for confounders. Heterogeneity was also shown in the statistical analysis used, outcome evaluated, study participants and setting. Studies with non-English language and other unpublished studies or 'grey' literature were not included in this review so this could potentially result in publication bias. Publication bias (a type of reporting bias) arises because statistically significant results (usually from large studies) are more likely to be published than non-significant results (usually small studies)[158]. It is most commonly tested using e.g. funnel plot but in this review it was not produced as it is usually performed as part of a meta-analysis and because of the time constraint of this research project. Finally, some of the included studies did not adjust for potential confounders such as smoking and alcohol intake and this could be a source of bias in these studies. A possible solution would be to conduct a multivariate analyses (i.e. controlling for at least one other association) or by excluding articles that did not adjust for these factors.

Although this review has several limitations, it has also important strengths. This study is the first and most comprehensive systematic review in the literature to extensively evaluate non-genetic risk factors for DD. Robust methodology compliant with the Cochrane handbook for systematic reviews[159] was used in this

review in all its stages. The literature was extensively searched using all databases, so comprehensive appraisal of the literature was achieved. The EPHPP is a standardised tool that has been shown to be valid and reliable measure of the quality and risk of bias of quantitative studies[160]. In the included studies, most DD cases were diagnosed by doctors so accurate case selection was assured. This study is of high clinical importance as it raises the awareness of clinicians and patients of these associations. It also has a direct clinical relevance, as it will encourage general practitioners and other physicians to look for and treat modifiable risk factors such as diabetes, hypertension and hyperlipidaemia in patients presenting with DD. Furthermore, the results can be used to encourage lifestyle changes in patients with regards to other modifiable lifestyle factors such as alcohol consumption, smoking and potentially manual work exposure.

2.1.3 Future work:

My recommendation for future work would be to conduct sub-group meta-analyses of each studied association to give more accurate and robust summary estimate of their statistical evidence. A further interesting avenue would be a systematic review of genetic associations for DD development and progression. It would be interesting to look at recent population-based twin studies and genome-wide association studies that evaluated the genetic predisposition to DD[3,161–163]. More robust prospective cohort studies e.g. using real world data such as CPRD dataset and UK Biobank are needed to clarify the causal relationship of these associations with DD.

2.6 Conclusion

DD has multiple non-genetic associations reported in the literature. Despite conflicting evidence, this study showed a strong association between DD and advanced age, male gender, family history of DD and DM. Furthermore, heavy alcohol drinking, cigarette smoking and manual work exposure showed a positive dose-response relationship. The evidence for the remaining factors was weak or inconclusive. Further high-quality prospective studies are needed to explain the causal pathway for these associations and sub-group meta-analyses are necessary to determine the association with more accuracy.

2.7 Chapter appendix

Table 1: Literature search strategy and keywords using PECOS analysis

PECOS elements	**Definition**	**Main search keywords for the search databases:** Ovid Medline, Ovid Embase, Scopus, Web of Science Core Collection, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials
Population	Patients with DD	(("Dupuytren Contracture"[Mesh]) OR dupuytren*[Title/Abstract]) OR palmar fascia[Title/Abstract]) OR palmar fibromatosis[Title/Abstract]) OR viking disease[Title/Abstract]) OR palmar fascial fibromatosis[Title/Abstract]))
Exposure	Any variable which has been assessed as a potential non-genetic risk factor for the development of DD	risk factors OR (risk* or factor* or develop*).ti,ab.OR exp disease progression OR exp Diabetes Mellitus OR exp EPILEPSY OR exp Smoking OR exp Alcohol Drinking OR exp Anticonvulsants OR exp Arthritis, Rheumatoid OR body mass index OR exp Ethnic Groups OR Hypercholesterolemia OR timolol.ti,ab. OR "insulin-depend*".ti,ab. OR diabet*.ti,ab. OR epilep*.ti,ab. OR (hypertension or hypertensive).ti,ab. OR "high blood pressure".ti,ab. OR smok*.ti,ab. OR

		alcohol*.ti,ab. OR age*.ti,ab. OR gender*.ti,ab. OR (male or males).ti,ab. OR trauma*.ti,ab. OR occupation*.ti,ab. OR "anti-epileptic*".ti,ab. OR anticonvulsant*.ti,ab. OR "anti-convulsant*".ti,ab. OR "rheumatoid arthritis".ti,ab. OR (low* adj2 (BMI or "body mass")).ti,ab. OR ethnicity.ti,ab. OR hypercholest*.ti,ab.
Comparisons	Control group (Patients without DD or no exposure as defined in the study)	Checked manually during abstract and full-text screening
Outcomes	Development of DD	For prospective studies only (as defined in the Population element)
Study design	All Included:- Screen literature search results manually according to the PRISMA guideline (abstract and then full-text). Inclusion Criteria: Observational studies (Case control studies	-Exclude: animal* OR cadaver* OR cell).ti,ab. -Limit search to English language publications

	and cohort studies) Interventional studies including RCTs Exclusion Criteria: No comparator group Publication not written in English, Case reports, case series, conference abstracts, letters to editor, animal studies, cell studies, cadaver studies	

Detailed search strategies (26/11/18)

1. **Medline database** (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®):1946 to present:

1 Dupuytren Contracture/ (2554)

2 dupuytren*.ti,ab. (2698)

3 "palmar fascia".ti,ab. (254)

4 "palmar fibromatosis".ti,ab. (74)

5 "viking* disease".ti,ab. (4)

6 "palmar fascial fibromatosis".ti,ab. (1)

7 1 or 2 or 3 or 4 or 5 or 6 (3205)

8 risk factors/ (745099)

9 (risk* or factor* or develop*).ti,ab. (7087301)

10 exp disease progression/ (159454)

11 exp Diabetes Mellitus/ (391760)

12 exp EPILEPSY/ (104670)

13 exp Smoking/ (138215)

14 exp Alcohol Drinking/ (63897)

15 exp Anticonvulsants/ (132336)

16 exp Arthritis, Rheumatoid/ (106865)

17 body mass index/ (113619)

18 exp Ethnic Groups/ (141313)

19 Hypercholesterolemia/ (24849)

20 timolol.ti,ab. (4174)

21 "insulin-depend*".ti,ab. (29000)

22 diabet*.ti,ab. (562516)

23 epilep*.ti,ab. (124616)

24 (hypertension or hypertensive).ti,ab. (394898)

25 "high blood pressure".ti,ab. (13610)

26 smok*.ti,ab. (253491)

27 alcohol*.ti,ab. (302502)

28 age*.ti,ab. (3336882)

29 gender*.ti,ab. (288422)

30 (male or males).ti,ab. (1016141)

31 trauma*.ti,ab. (326793)

32 occupation*.ti,ab. (142672)

33 "anti-epileptic*".ti,ab. (3334)

34 anticonvulsant*.ti,ab. (21139)

35 "anti-convulsant*".ti,ab. (712)

36 "rheumatoid arthritis".ti,ab. (97052)

37 (low* adj2 (BMI or "body mass")).ti,ab. (11641)

38 ethnicity.ti,ab. (56542)

39 hypercholest*.ti,ab. (33476)

40 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (10712079)

41 7 and 40 (1119)

42 (animal* or cadaver* or cell).ti,ab. (3946687)

43 41 not 42 (1017)

44 43 (1017)

45 limit 44 to english language (777)

2. **Embase database:** 1974 to present:

1 Dupuytren Contracture/ (2840)

2 dupuytren*.ti,ab. (2573)

3 "palmar fascia".ti,ab. (289)

4 "palmar fibromatosis".ti,ab. (84)

5 "viking* disease".ti,ab. (2)

6 "palmar fascial fibromatosis".ti,ab. (1)

7 1 or 2 or 3 or 4 or 5 or 6 (3266)

8 risk factors/ (526086)

9 (risk* or factor* or develop*).ti,ab. (9058259)

10 disease exacerbation/ (83690)

11 exp diabetes mellitus/ (845630)

12 exp epilepsy/ (212774)

13 exp smoking/ (346459)

14 drinking behavior/ (44746)

15 exp anticonvulsive agent/ (372468)

16 exp rheumatoid arthritis/ (182250)

17 body mass/ (300237)

18 exp ethnic group/ or ethnicity/ (180239)

19 exp hypercholesterolemia/ (65222)

20 timolol.ti,ab. (5151)

21 "insulin-depend*".ti,ab. (34245)

22 diabet*.ti,ab. (823018)

23 epilep*.ti,ab. (173477)

24 (hypertension or hypertensive).ti,ab. (572446)

25 "high blood pressure".ti,ab. (19836)

26 smok*.ti,ab. (363210)

27 alcohol*.ti,ab. (403831)

28 age*.ti,ab. (4761198)

29 gender*.ti,ab. (457662)

30 (male or males).ti,ab. (1522399)

31 trauma*.ti,ab. (409910)

32 occupation*.ti,ab. (175052)

33 "anti-epileptic*".ti,ab. (6151)

34 anticonvulsant*.ti,ab. (28551)

35 "anti-convulsant*".ti,ab. (1216)

36 "rheumatoid arthritis".ti,ab. (139515)

37 (low* adj2 (BMI or "body mass")).ti,ab. (19241)

38 ethnicity.ti,ab. (83373)

39 hypercholest*.ti,ab. (45695)

40 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (13758587)

41 7 and 40 (1547)

42 (animal* or cadaver* or cell).ti,ab. (4825554)

43 41 not 42 (1379)

44 43 (1379)

45 limit 44 to english language (1081)

3. Scopus database:

((TITLE-ABS-KEY (dupuytren* OR "palmar fascia" OR "palmar fibromatosis" OR "viking* disease" OR "palmar fascial fibromatosis")) AND ((TITLE-ABS-KEY (risk* OR factor* OR develop*)) OR (TITLE-ABS-KEY (disease* W/2 progress*)) OR (TITLE-ABS-KEY ((timolol OR "insulin-depend*" OR diabet* OR epilep* OR hypertension OR hypertensive OR "high blood pressure"))) OR (TITLE-ABS-KEY ((smok* OR alcohol* OR age* OR gender* OR male OR males OR trauma* OR occupation* OR "anti-epileptic*" OR anticonvulsant* OR "anti-convulsant*"))) OR (TITLE-ABS-KEY (("rheumatoid arthritis" OR (low W/2 (bmi OR "body mass")) OR ethnicity OR "ethnic group*" OR hypercholest*))))) AND NOT (TITLE-

ABS-KEY (animal* OR cadaver* OR cell)) AND (LIMIT-TO (LANGUAGE , "English"))

4. **Web of Science database:**

1 2,257 TOPIC: (dupuytren* OR "palmar fascia" OR "palmar fibromatosis" OR "viking* disease" OR "palmar fascial fibromatosis")

2 12,598,917 TOPIC: (risk* OR factor* OR develop*)

3 129,424 TOPIC: (disease* near/2 progress*)

4 1,252,706 TOPIC: (timolol OR "insulin-depend*" OR diabet* OR epilep* OR hypertension OR hypertensive OR "high blood pressure")

5 5,972,839 TOPIC: (smok* OR alcohol* OR age* OR gender* OR male OR males OR trauma* OR occupation* OR "anti-epileptic*" OR anticonvulsant* OR "anti-convulsant*")

6 340,931 TOPIC: ("rheumatoid arthritis" OR (low near/2 (bmi OR "body mass")) OR ethnicity OR "ethnic group*" OR hypercholest*)

7 16,932,239 #6 OR #5 OR #4 OR #3 OR #2

8 902 #7 AND #1

9 822 #7 AND #1 Refined by: LANGUAGES: (ENGLISH)

Search Strategy (27/11/18)

5. **Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2018:

#1 MeSH descriptor: [Dupuytren Contracture] explode all trees 81

#2 dupuytren* 194

#3 "palmar fascia" 13

#4 "palmar fibromatosis" 1

#5 "viking* disease" 1

#6 "palmar fascial fibromatosis" 0

#7 #1 or #2 or #3 or #4 or #5 or #6 197

#8 MeSH descriptor: [Disease Progression] explode all trees 6653

#9 MeSH descriptor: [Risk Factors] explode all trees 23273

#10 MeSH descriptor: [Diabetes Mellitus] explode all trees 25903

#11 MeSH descriptor: [Epilepsy] explode all trees 2144

#12 MeSH descriptor: [Smoking] explode all trees 5679

#13 MeSH descriptor: [Alcohol Drinking] explode all trees 3404

#14 MeSH descriptor: [Anticonvulsants] explode all trees 2264

#15 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 5277

#16 MeSH descriptor: [Body Mass Index] explode all trees 9253

#17 MeSH descriptor: [Ethnic Groups] explode all trees 3905

#18 MeSH descriptor: [Hypercholesterolemia] explode all trees 3075

#19 risk* or factor* or develop* 401343

#20 disease* near/2 progress* 18520

#21 timolol OR "insulin-depend*" OR diabet* OR epilep* OR hypertension OR hypertensive OR "high blood pressure" 119002

#22 smok* OR alcohol* OR age* OR gender* OR male OR males OR trauma* OR occupation* OR "anti-epileptic*" OR anticonvulsant* OR "anti-convulsant*" 779607

#23 "rheumatoid arthritis" OR ethnicity OR "ethnic group*" OR hypercholest* 22823

#24 low* near/2 (bmi OR "body mass") 1153

#25 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 899318

#26 #7 and #25 159

Chapter 3. Dupuytren's disease (DD) patients' characteristics and surgical treatment pathway

3.1 Introduction

As discussed in Chapter 1, it is known that DD most commonly affects the white, male, elderly population of northern European origin and their descendants[18]. However, few large scale population-based studies have evaluated characteristics of DD patients who had surgical treatment. In particular, there is a scarcity of data on the presence of socio-economic deprivation and comorbidity in previous epidemiological studies evaluating surgically treated DD patients. Patients with DD who need surgery may receive one surgical procedure (primary surgery only) or require another procedure on the same hand (reoperation or revision). Furthermore, as discussed in Chapter 1, there are broadly three types of operations for DD – percutaneous needle fasciotomy (PNF), limited fasciectomy (LF), and dermofasciectomy (DF). Each option is available for either primary surgery or for re-operation, and they are thought to have different recurrence and complication rates. The DD surgical treatment pathway is not well described in the literature in terms of the frequency and proportion of each procedure in the population and the type of surgery in each pathway.

3.1.1 Aims:

The primary aim of this chapter was to describe DD patients' characteristics in terms of age, gender, ethnicity, index of multiple deprivation (IMD) and Charlson Comorbidity Index. The secondary aim was to describe the surgical treatment pathway that DD surgical patients followed, and the sequence of procedures followed when reoperation was needed.

3.2 Methods

3.2.1 Study design

A longitudinal nationwide cohort study was conducted from the prospectively collected Admitted Patient Care (APC) episodes of the Hospital Episode Statistics (HES) dataset.

3.2.2 Data extraction and cleaning

I extracted the APC subset data from the HES dataset using ICD-10 and OPCS-4 codes (see full list of codes in table 1 in the Appendix (see3.6)). The studied primary DD surgical procedures were grouped into percutaneous needle fasciotomy (PNF), limited fasciectomy (LF) and dermofasciectomy (DF). Within OPCS, revision procedure codes are only available for revision LF and revision DF. Someone having a second operation on the same hand that is coded as a primary procedure in OPCS might be undergoing true primary surgery on a different finger (finger specific codes are not available), or true revision surgery following a primary procedure. Therefore, I decided to use the term ‘reoperation’ to describe further surgery on the same hand, instead of revision. Reoperation is defined in this study as any surgical procedure done on the same hand following the primary procedure.

Patients’ demographics were processed and grouped into more clinically relevant categories. Age was grouped in 5-year bands with the exception of the first band (18 to less than 20 years old) and the final band (age 85 and older). Ethnicity was grouped as White, Asian, Black, mixed ethnicity, any other ethnicity and unknown ethnicity (missing), as shown in table 2 in the Appendix (see 3.6).

3.2.3 Data analysis

I used descriptive analysis to report demographics of patients who had surgery for DD in terms of age at time of operation, gender, ethnicity, and their IMD. The IMD is an indicator of relative socioeconomic deprivation of small geographical areas in England; the Lower-layer Super Output Areas (LSOA)[164]. IMD may inform us about employment factors pre-disposing to DD, or the disparities in accessing surgical care among patients. IMD was divided into 10 deciles as shown in table 3 in the Appendix (see 3.6). Charlson Comorbidity Index describes comorbid illnesses in patients undergoing surgical treatments. It is vital for evaluating the number and seriousness of these comorbidities on the risks of surgery[165]. Charlson Comorbidity Index was calculated from episodes up to and including each index episode and using the 12-comorbidity modified index described by Quan *et al*[166]. Except for ethnicity, missing data from demographic variables were less than 1% in most of my results and considered to be 'missing completely at random'. Therefore missing data were excluded from the analysis - complete cases analysis approach.

I described the surgical treatment pathway of 99.31% of the DD surgical operations with non-missing side code (missing was 2,576/158,119=1.63%) included in the study and summarised it in a sunburst chart produced using Microsoft Excel. I used Stata MP (StataCorp. 2017. Stata Statistical Software: v15. College Station, TX: StataCorp LLC) for data cleaning and analysis.

3.3 Results

3.3.1 Participants

Between 1 April 2007 and 31 March 2017, 158,119 DD operative procedures were performed in 121,488 adult patients and included in the analysis. The original HES APC data contained 1,825,242 admitted patient episodes relating to DD diagnosis, DD surgical treatment, its complications and patients' comorbidities. I first collapsed the data to one line per procedure (total=264,269); these procedures were linked with DD using OPCS-4 codes. In the collapsed file, 2,146 procedures were excluded; 2,141 were operations done for non-DD indications, for example fasciotomy to treat compartment syndrome. The remaining 5 procedures were performed for paediatric cases, defined as age less than 18. After the initial exclusion, the number of procedures was expanded from 262,123 to 265,431 procedures after identifying bilateral cases and moving one of each procedure into a separate line. An additional 107,312 procedures were excluded from the dataset as they were performed before the 2007-2008 financial year. The reason for exclusion is that before the 2007-2008 financial year, the OPCS coding system (v4.3 and v4.4) used the code (T528) for multiple procedures (digital fasciectomy and its revision, dermofasciectomy and its revision, 'other specified excision of other fascia' and 'other specified other excision of other fascia'). From 2008 onward (OPCS v4.5, v4.6 and v4.7), these procedures were coded separately and therefore the coding system became more accurate. The final data file used to report patients' demographics was produced after collapsing the procedure file to one line per patient.

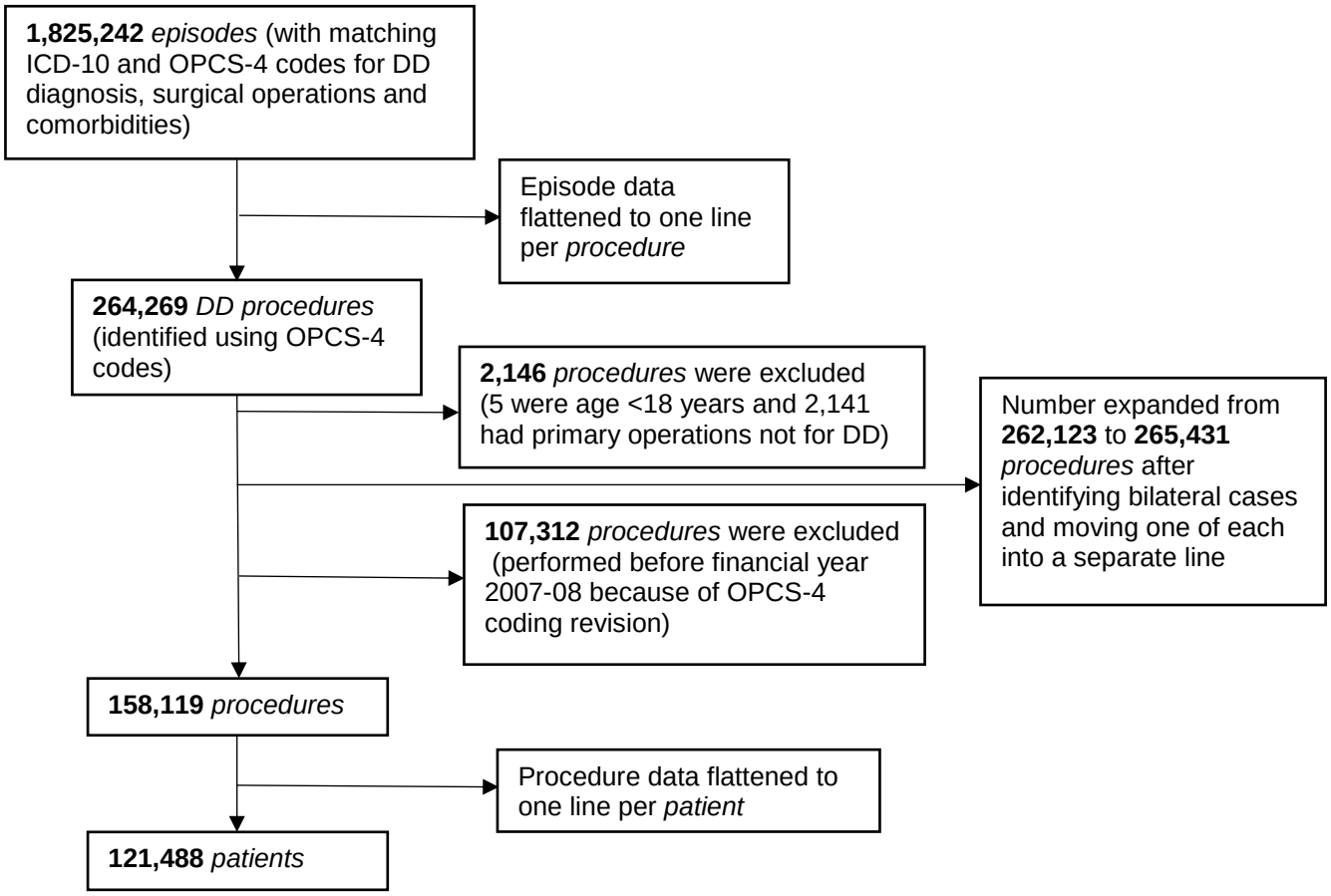


Figure 1: Data cleaning flowchart

3.3.2 Patients' characteristics

The mean (SD) age of patients at the time of surgery was 65.5 (10.67) years. It ranged from 18 to 111 years and the majority of patients were in the 65 to <70 years group. The majority of patients were male (n=94,458/121,422[e], 77.8%), while females accounted for 26,984/121,422[e], (22.2%) giving a male-to-female ratio of ~3.5:1. There was a very similar age distribution of male and female patients (Figure 2).

[e] Indicating denominator after excluding missing data

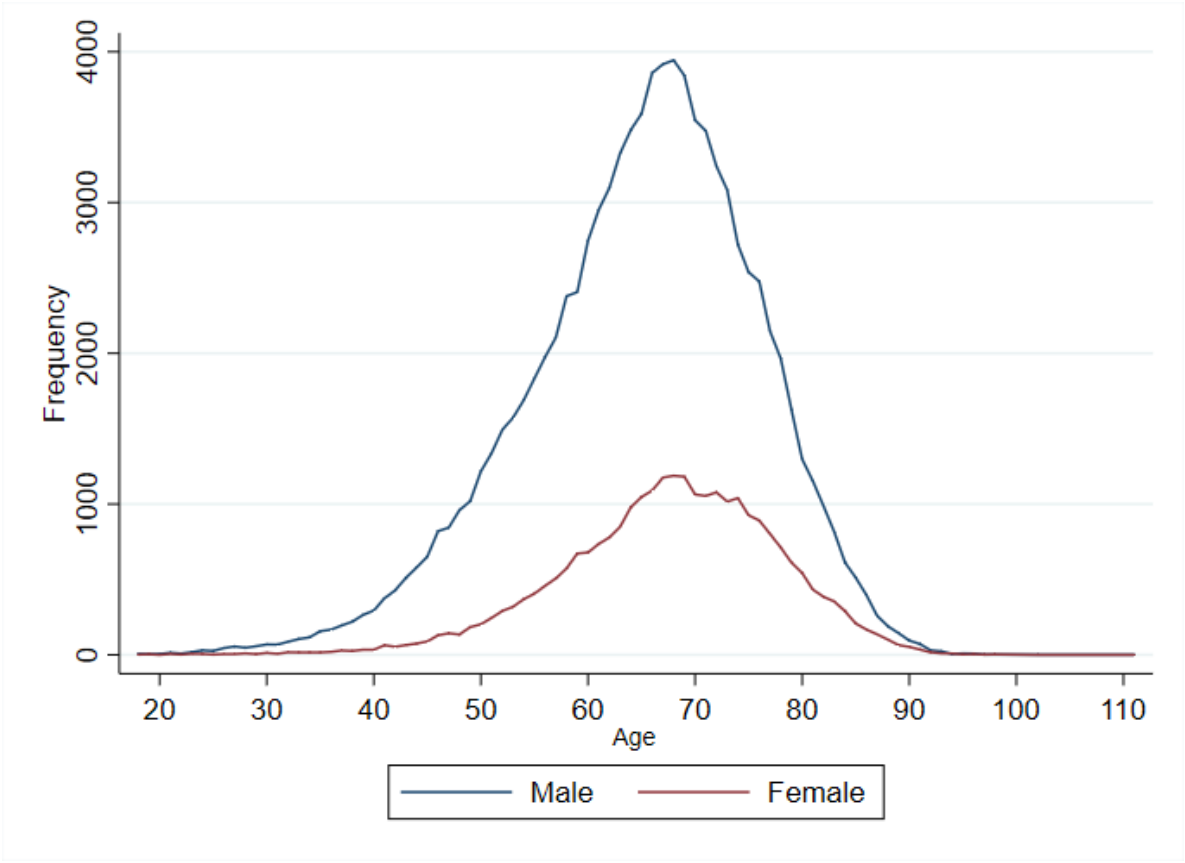


Figure 2: Kernel density plot showing the age distribution (continuous) across both genders in patients who had DD surgery in England in financial years (2007/2008-2016/2017)

As shown in table 2 in the Appendix (see 3.6), 11.64% of ethnicities were missing. Of the remaining 107,350 patients, 105,822 had a white ethnic background (98.58%), with the remaining 1.42% coming from a variety of ethnic minorities (Asian, Black, mixed ethnicity and other ethnicities). Most patients lived in less deprived areas; the largest group of patients was in the less deprived (20-30%) IMD decile (Figure 3 and table 3 in the Appendix (see 3.6)). The median (IQR) of Charlson Comorbidity Index for all surgical procedures was 0 (0-1).

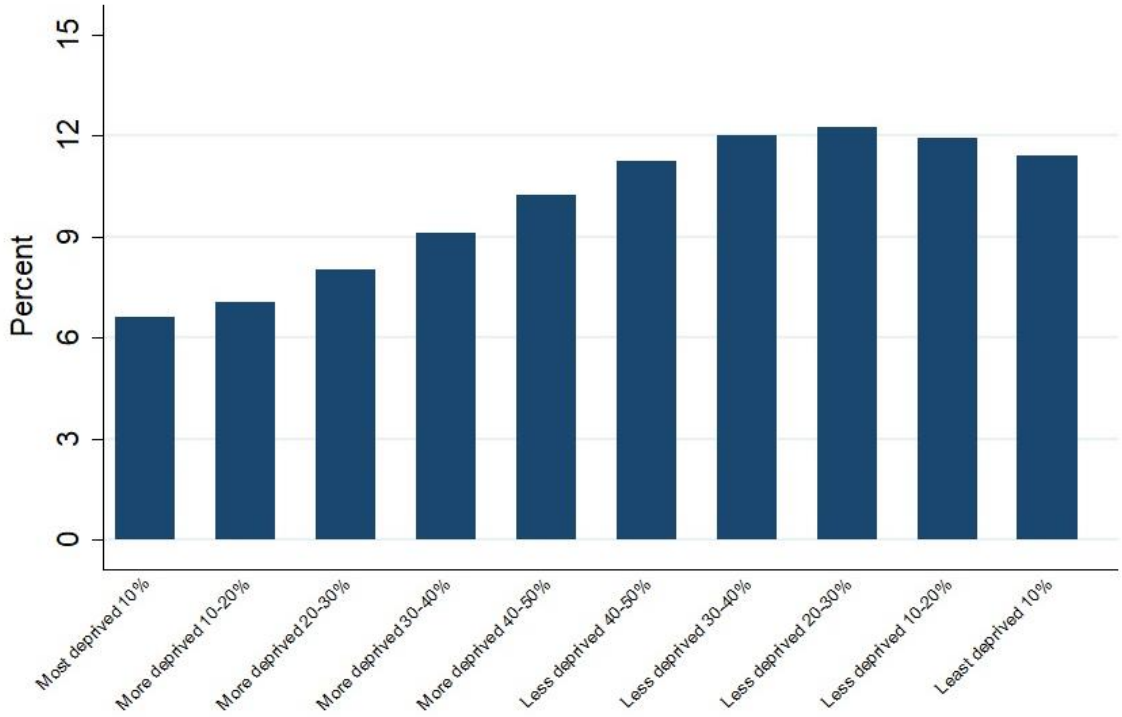


Figure 3: Index of Multiple Deprivation (IMD) deciles of patients who had DD surgery in England in financial years 2007/2008-2016/2017

3.3.3 Surgical treatment pathway

I analysed the most common surgical treatment pathways that were undertaken for each hand. Pathways with a frequency of less than 100 procedures in the ten-year period were excluded (0.7%) to simplify the analysis. As shown in Figure 4 below and table 4 in the Appendix (see 3.6), 154,450 (99.3%) of DD surgical treatment for each hand followed one of 20 distinct pathways. Most of the included hands (n=125,944; 81.54%) had primary operations only; most commonly LF (n=109,933; 87.29%), followed by PNF (10,546; 8.37%) and lastly DF (5,465; 4.34%). The remaining hands (n=28,506; 18.46%) underwent reoperation. The majority of the reoperations (21,075; 73.93%) were a repeat of the primary operation, for example repeat LF once or twice after primary LF. The

remaining reoperations (7,431, 26.07%) followed less common minor pathways. Most of these other reoperation pathways (5,751 hands; 77.39%) followed increasing invasiveness – for example PNF was followed by LF or DF; LF was followed by DF. The remaining pathways followed sequences whereby more invasive procedures were followed by less invasive procedures, for example LF followed by PNF, or DF followed by LF. These pathways accounted for 1,680 (22.61%) of hands.

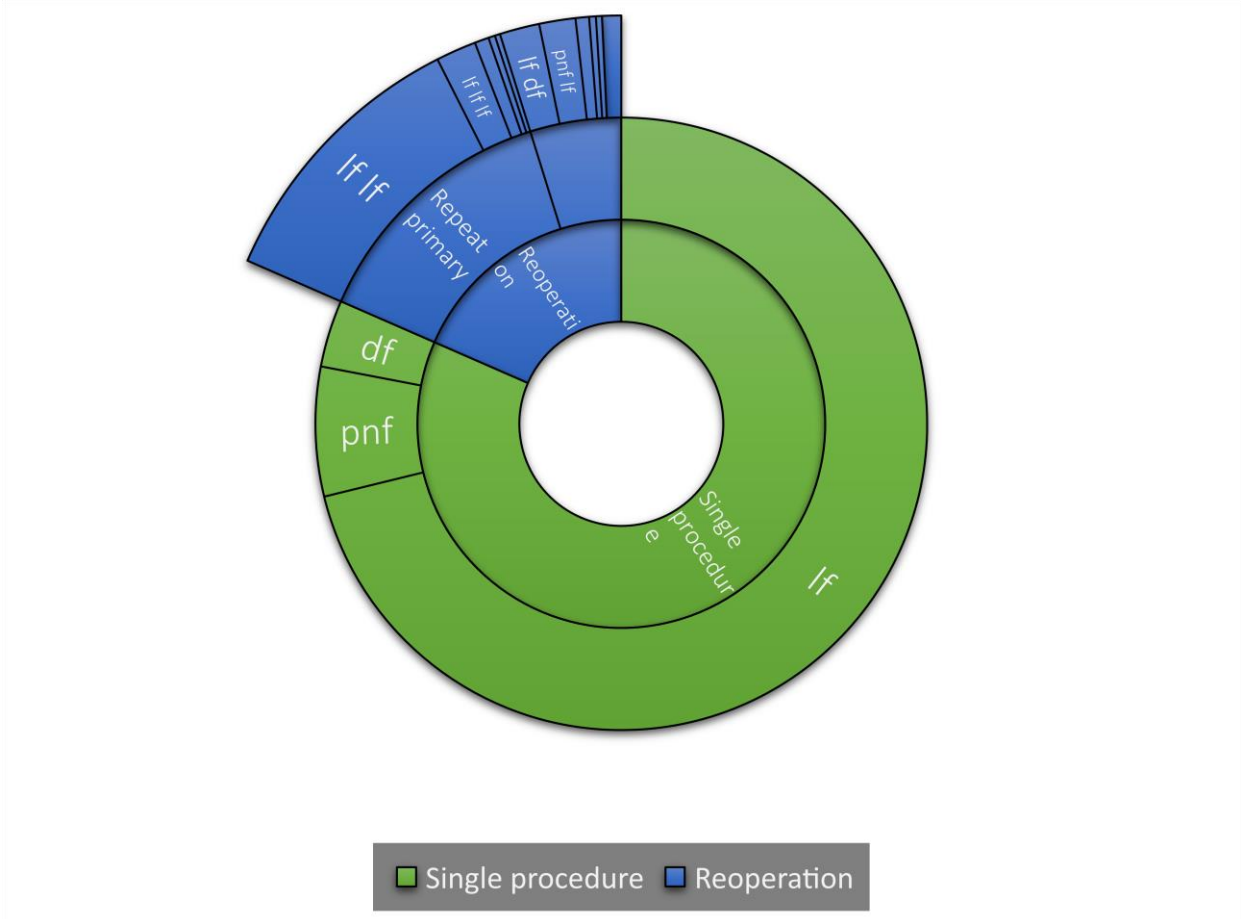


Figure 4: Sunburst chart showing treatment pathways of DD surgery in England (2007/2008-2016/2017)

3.4 Discussion

In this study, the results show that DD surgery follows a similar pattern to the DD demographics reported in the literature, in which the disease usually affects the

elderly, males, and the white population. One previous study[167] looked at the age and gender of DD patients who had surgical treatment; males were three times more than females (ratio=3:1) and this ratio is very similar to my study population's gender ratio (~3.5:1). They have also found that most patients who had their condition surgically treated were elderly, in the range of 60 to 64 years old, which is again very close to my results (65-69 years old).

People in the less deprived categories of IMD, meaning those who have a better socioeconomic status, were more likely to undergo DD surgery compared to those who were more deprived. This disparity could be interpreted in two ways. First, less deprived people could have better access to healthcare and therefore be more likely to receive surgical treatment for their condition compared to the more deprived people. In support of this interpretation, a similar pattern to my results was observed in the rates of hip and knee replacement surgery in NHS England[168]. Second, the finding that the majority of DD surgical patients were less deprived might contradict the long-believed theory that DD disease is more common in manual workers, who are typically more deprived. A similar finding was observed by Khan *et al*[156] in which they looked at that rates of DD in male patients who presented to primary care centres in England and Wales. They found that the rates were higher in non-manual occupational social class compared to manual workers. Inequality in accessing surgical care in fact exists among countries, particularly low-to-middle-income countries compared to high-income countries and also within each country[169]. It is interesting to observe that even in England, a high-income country, potential inequality in accessing surgical care is evident from my results.

Although patients with DD, including in this cohort, are elderly with an expected high number of comorbidities, my cohort overall had a low Charlson Comorbidity Index. It is expected that patients who are selected to have surgery are more likely to be relatively fit and healthy.

3.4.1 Limitations and strengths

As HES consists of routinely collected data, it's subject to coding errors and inaccuracy. Coding of patients' data such as diagnoses and operations is usually done by non-medical coders, and clinicians are not usually involved in the process [170]. However, the coding accuracy of routinely collected data such as HES has improved in the last few years as there are more financial incentives for hospitals to improve their coding to insure more accurate remuneration[96,171]. I have not specifically studied the accuracy of coding practice by checking for the coding of individual operations in patient notes, and so misclassification remains a potential weakness of this study, and this coding validation should form part of future research on this topic.

The use of the term reoperation in the treatment pathway does not necessarily reflect the true picture of revision surgery. HES contains operative (OPCS) codes for some DD revision surgery such as revision LF (T522 and T526) and revision DF (T562). However, this is not the case for other types of DD surgery including PNF, where there is no specific revision code, so revision operations are coded with a further primary operative code. In addition, the lack of specific anatomical codes for each finger made it impossible to evaluate revision surgery with accuracy – I was unable to distinguish between a further operation on the little finger, and an operation on the index finger of the same hand, for example.

However, the use of the term ‘reoperation’ in this study as any subsequent DD surgery on the same hand, is a good alterative that accurately describes the surgical treatments captured in HES. In addition, for patients having a further operation on a particular hand is likely to still be clinically meaningful, meaning these results, and those in subsequent chapters, will still apply practically in a clinical situation.

To my knowledge, this is the largest population-based DD study published in the literature with a long observation period (10 years). It has also a low proportion of missing data (except for ethnicity) meaning that the results are more likely to be generalisable and representative of DD patients in England. However, the entire population of patients undergoing DD surgery has not been captured. For example, some patients have received their surgical treatment in private hospitals that are not part of the NHS, and therefore these cases are not reported in HES dataset. It is likely that this population is even less deprived than those accessing healthcare through the NHS.

3.4.2 Future work

Having studied the surgical treatment of DD, it would be prudent to study DD in the overall population. The APC HES data can be linked to other real world data that contains outpatient information concerning DD patients such as the Clinical Practice Research Datalink (CPRD) dataset and private clinics. Linking inpatient and outpatient datasets can give a broader picture of patient demographics, treatment pathway, and other clinical findings discussed in the subsequent chapters of this thesis. The treatment pathway of DD surgical procedures can be studied further by identifying the most common pathways in patients instead of

surgical operations. Finally, the findings of this thesis can be used in the future to assist in cost effectiveness studies and economic modelling of surgical treatment of DD.

3.5 Conclusion

DD surgery in England was most commonly performed in male, elderly, white patients with less financial deprivation and few comorbidities. Most operations performed were primary procedures with LF being the most common type of primary surgery. Some patients required reoperation and most had a repeat of their primary procedure.

3.6 Chapter appendix

Table 1: DD diagnostic (ICD v10) and operative codes (OPCS v4.4, 4.5, 4.6, 4.7) for surgical treatment

Grouping	Condition	OPCS-4 code		ICD-10 code
DD	Palmar fascial fibromatosis			M720
LF	Palmar fasciectomy	T521		
	Revision of palmar fasciectomy	T522		
	Digital fasciectomy	T525		
	Revision of digital fasciectomy	T526		
DF	Dermofasciectomy	T561		
	Revision of dermofasciectomy	T562		
PNF	Division of palmar fascia	T541		
	Other specified division of fascia	T548	Linked with (+)	M720
	Unspecified division of fascia	T549		
	Other specified release of fascia	T558		
	Unspecified release of fascia	T559		
LF	Other specified excision of other fascia	T528		
	Unspecified excision of other fascia	T529		
	Other specified other excision of other fascia	T568		
	Unspecified other excision of other fascia	T569		
Anatomical codes	Hand NEC	Z894		
	Thumb NEC	Z895		
	Finger NEC	Z896		
	Multiple digits of hand NEC	Z897		
	Skin of finger	Z503		
	Bilateral operation	Z941		
	Right sided operation	Z942		
	Left sided operation	Z943		
	Unilateral sided operation	Z944		
	Specified laterality NEC	Z948		
	Laterality NEC	Z949		

Table 2: Ethnicity grouping and frequency of each ethnic category

Grouped ethnicity	Original categories	Frequency*
White	British (White), Irish (White), any other white background	105,822 (98.58%)
Asian	Indian, Indian (Asian or Asian British), Bangladeshi, Bangladeshi (Asian or Asian British), Pakistani, Chinese, Chinese (other ethnic group), any other Asian background	589 (0.55%)
Black	Black (Caribbean), Black (African), Caribbean (Black or Black British), African (Black or Black British), any other Black background	357 (0.33%)
Mixed ethnicity	Any other mixed background , White and Black Caribbean (Mixed), White and Black African (Mixed), White and Asian (Mixed)	159 (0.15%)
Any other ethnicity	Any other ethnicity	423 (0.39%)
Unknown ethnicity (missing)	Not given, not stated, not known	14,138 (11.64%)
Total		121,488 (100%)

*Denominator for all groups except missing=107,350 (total without missing observations)

Table 3: Index of multiple deprivation (IMD) deciles

IMD deciles	Number of patients	Frequency (%)*
Least deprived 10% (Decile 1)	13,715	11.4
Less deprived 10-20% (Decile 2)	14,383	11.9
Less deprived 20-30% (Decile 3)	14,764	12.3
Less deprived 30-40% (Decile 4)	14,442	12.0
Less deprived 40-50% (Decile 5)	13,564	11.3
More deprived 40-50% (Decile 6)	12,349	10.3

More deprived 30-40% (Decile 7)	10,958	9.1
More deprived 20-30% (Decile 8)	9,686	8.0
More deprived 10-20% (Decile 9)	8,520	7.1
Most deprived 10% (Decile 10)	7,983	6.6
Missing	1,124	0.93**
Total	121,488	100**

*Denominator=120,364 (total without missing IMD deciles).
**Denominator=121,488

Table 4: Surgical treatment pathway for most (99.31%) of the DD surgical procedures

Category	Subcategory	Procedure	Number	%
Single procedure		PNF	10,546	6.8
		LF	109,933	71.3
		DF	5,465	3.5
Reoperation	Repeat primary	PNF, PNF	872	0.6
		LF, LF	17,008	11
		LF, LF, LF	2,470	1.6
		LF, LF, LF, LF	405	0.26
		DF, DF	320	0.21
	Other reoperations	LF, DF	2,440	1.58
		PNF, LF	2,217	1.44
		LF, LF, DF	412	0.3
		PNF, LF, LF	205	0.1
		PNF, DF	199	0.1
		PNF, PNF, DF	165	0.1
		LF, DF, DF	113	0.1

		LF, PNF	824	0.5
		DF, LF	366	0.2
		LF, PNF, LF	202	0.1
		LF, DF, LF	187	0.1
		LF, LF, PNF	101	0.1
Total			154,450	100

Chapter 4. DD postoperative complications and rate of reoperations

4.1 Introduction

As discussed in Chapter 1, surgery is the mainstay treatment option for Dupuytren's disease (DD). As in any surgical procedure, DD surgery carries potential risks of local and systemic complications in addition to risk of reoperation following primary surgery. Very few large-scale studies have evaluated the risk of postoperative complications or reoperations. Most of these studies were case series reported from a single institution. For instance, Khan *et al*[172] performed LF (n=27) and DF (n=3) in 30 DD hands and found an overall local complications (oedema, stiffness, surgical site infection, haematoma and recurrence) rate of ~ 17% after a maximum follow-up period of 5 years. Similarly, McFarlane *et al*[173] reported an overall risk of local complications of 17% following DD surgery in 1339 patients. Rodrigo et al[174] reported a reoperation (due to recurrence) rate of 15% following LF in 65 hands and 43% following open fasciotomy in 41 hands. In a series of 253 DD patients treated with LF, Bulstrode et al[175] found a complication rate of ~ 18%. Of which three cases (1.2% of total patients) had systemic complications (urinary retention, MI and congestive heart failure). To my knowledge, no other published studies have examined the incidence of systemic complications following DD surgery. In a survey-based chart review study from 12 European counties, Bainbridge et al[176] reported an overall intraoperative local complication rate of 4% and postoperative rate of 23% in 3,357 patients treated surgically for DD. No other larger-scale population based studies could be found in the literature reporting on complication rates after DD surgery. There is a need for nation-wide multi-centre studies to

investigate these complications. It's important for patients and surgeons to be aware of the risk of these complications and to be informed and counselled before surgery so they can make an informed decision. It’s also vital for surgeons to be mindful of the possibility of their occurrence and to try to mitigate these adverse events by providing optimal perioperative care. Finally, general practitioners and any physicians involved in the medical management of DD and responsible for referrals to secondary or tertiary care should also be aware of these complications.

4.1.1 Aims:

The primary aim of this chapter was to estimate the incidence of local and serious systemic complications 30 and 90 days after DD surgery. To assess this aim, two methods were used; cumulative incidence to estimate the local and serious systemic complications, and a self-controlled case series method to evaluate serious systemic complications. Secondary aim was to evaluate the rate and some determinants[f] of the first reoperation following primary DD surgery using survival analysis method.

4.2 Methods

Hospital Episode Statistics-Admitted Patients Care (HES APC) dataset for all admitted episodes related to DD treatment and complications was linked with the Office for National Statistics (ONS) mortality data for the purpose of analysis of this chapter.

[f] An alternative to predictors or risk factors

4.2.1 Cumulative incidence of postoperative complications

Cumulative (unadjusted) incidence was calculated for local and serious systemic complications within 30 and 90 days after all DD surgery (primary and reoperations). These complications were necessarily severe enough to require re-admission to hospital to receive treatment, or they would not have been coded in HES APC. Admission is defined in HES APC dataset as: “any secondary care-based activity that requires a hospital bed, thus including both emergency and planned admissions and day cases”[96]. Both local and systemic complications evaluated in this study occurred from the same day of surgery up to 30 or 90 days after DD surgery. Local complications were defined as surgical site infection (SSI), neurovascular and tendon injury requiring surgical repair, and finger amputation, which occurred in the same operated hand. SSI was included if it required wound debridement and wound dehiscence if it required surgical closure. SSI and wound dehiscence were combined in one category “wound complications”. Serious systemic complications included stroke (excluding mini-stroke, or transient ischaemic attack), lower respiratory tract infection (LRTI), acute myocardial infarction (AMI), pulmonary embolism (PE), urinary tract infection (UTI), acute kidney injury (AKI), and death. As described in Chapter 1, ICD-10 and OPCS-4 codes were used to identify local and serious systemic postoperative complications in the dataset (see Table 1a and 1b in the Appendix). Operations with missing side code and operations that had less than 90 days follow-up after surgery (total n=7,286; 4.6%) were excluded from the analysis of local complications. For serious systemic complications, only operations with less than 90 days follow-up after surgery (n=4,743; 3%) were excluded from the analysis. Any number between 0 and 5 was suppressed to

comply with the HES and ONS disclosure policies[177]. Throughout this chapter, P value less than 0.05 was considered statistically significant and numbers were rounded off to two decimal places unless otherwise stated.

4.2.2 Self-controlled case series (SCCS)

The primary aim of this analysis was to estimate the relative incidence of serious systematic complications 90 days after first primary DD surgery compared to their baseline risk. Secondary aim was to estimate the same relative incidence but 30 days after first primary DD surgery. For this purpose, I used a self-controlled case series (SCCS) study design. SCCS design is a within-case comparison, requiring no separate comparator, i.e. each case acts as its own control to eliminate any time constant confounders[178]. It was initially used in vaccination safety studies and later in pharmaco-epidemiology and other clinical areas[179]. My analysis was limited to the first primary DD surgery that each patient had for two reasons. First, studying beyond the first primary DD surgery could result in an overlap between e.g. an exposure period of one surgery and a baseline period of another surgery. Second, some operations in my dataset (1.63%) had missing laterality codes so identifying subsequent surgery can be difficult. Figure 1 shows a schematic representation of the time intervals used in the SCCS method. The observation period was defined for 90-day adverse events as anytime between 180 days before surgery and 90 days backward (-180 to -270 days), and 90 days after surgery. For 30-day events, the observation period was defined from 180 days before surgery to 30 days backward (-180 to -210) and 30 days after surgery. Serious systemic complications occurred within 30 or 90 days after surgery (exposure risk period) were compared with each corresponding adverse event

occurred in the baseline risk period. The pre-operative baseline period was limited to 90 days in order to be equal to the post-operative (exposure risk) period. This is because the chance of experiencing a medical condition such as acute MI increases with an increasing period of observation, so the baseline and exposure risk periods must be of identical duration.

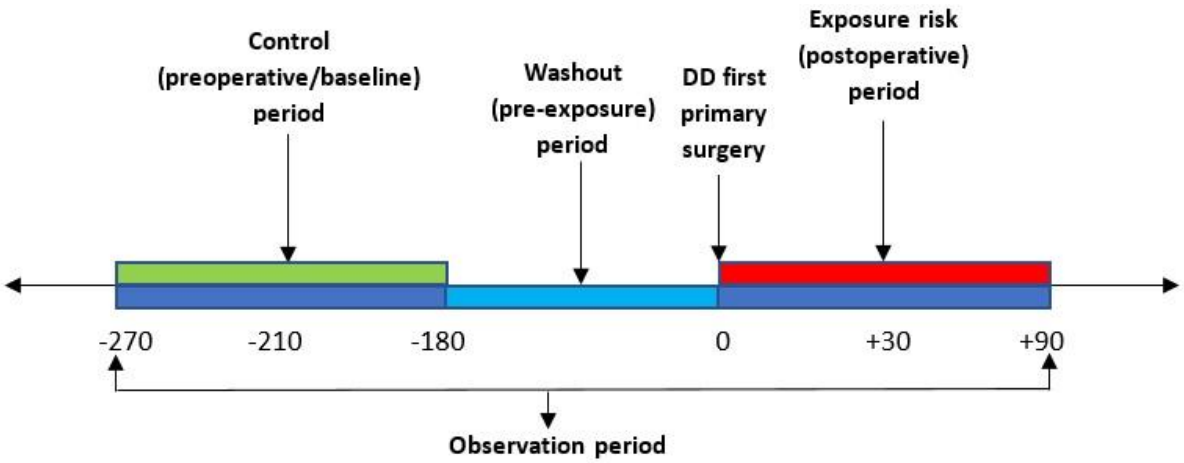


Figure 1: Schematic representation of the self-controlled Case Series (SCCS) model showing exposure risk period (red), control or baseline period (green), washout period (light blue) and observation periods (dark blue)

A washout (pre-exposure) period including the 6 months before surgery was used to comply with one of the key assumptions of the SCCS. i.e. the occurrence of an adverse event should not affect the probability of exposure[180]. In this case, the occurrence of any serious systemic adverse event can temporarily decrease the probability of having DD surgery i.e. cancellation or postponing the planned surgery to allow optimal recovery. Less than 1% of patients in my cohort died after surgery and prior to experiencing any systemic adverse events so I elected to not account for death in my analysis, as accounting for this low proportion in my analysis is unlikely to change the results found and would unnecessarily complicate the analysis. As the events in the SCCS must be independently recurrent, only the first adverse event after surgery was studied.

The analysis of the SCCS method was limited to cases with the outcomes of interest either in the 90-day window before surgery (baseline risk) or the 90-day window after surgery (exposure risk). As age is considered a time-varying confounder, although it has a minor effect here as the study time is relatively short, it was adjusted for by including it in the SCCS model. Age was categorised into 5-year bands starting from age 40 and ending with age 95 and above. The age bands between 40 and 59 were merged into one age band, and patients aged 90 and above were also combined into one band. The age band of 65 to 69 was taken as a reference category for the standard analysis. For two complications, AKI and PE, slightly different age categories were used due to a lower incidence of occurrence in younger and older patients and hence a lack of model convergence. For AKI, age bands from 40 to 69 were merged into one age band and the last band represented patients aged 85 and above. Age band (70 to 74) was used as a baseline for AKI. For PE, age bands from 40 to 65 were merged into one age band. Baseline for PE cohort was the same as the reference category (65 to 69).

Conditional Poisson regression offset by the natural logarithm of risk intervals was used to study the association between exposure to surgery and the occurrence of one of the serious adverse events within 30 or 90 days after surgery. The incidence rate ratio (IRR) and 95% CI were estimated for each adverse event. Interactions with gender and type of surgery (grouped according to presumed mode of anaesthesia – local anaesthetic for PNF; general or regional anaesthetic for LF and DF) were tested for each serious systemic complication after 90 days.

4.2.3 Survival analysis (time-to-first reoperation after primary DD surgery)

Kaplan Meier survival estimate was used to determine the cumulative probability of survival rate (time to reoperation) after primary surgery. The analysis was limited to the first reoperation following all primary DD surgery and after each subtypes of DD surgery (PNF, LF, and DF). Multivariable Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for each determinant of reoperation. Age (continuous variable), gender, grouped Charlson comorbidity index (0, 1, 2 or more) and IMD (10 deciles) were added to the Cox regression models as determinants.

4.2.3.1 Censoring

Operations were followed up from their index date (date of primary DD operation) until first reoperation on the same hand, death, loss-to follow-up or end of the study period (31st March 2017). Operations with missing side code (1.63%) were excluded from the analysis.

4.3 Results

4.3.1 Local and serious systemic postoperative complications

4.3.1.1 Local complications

As shown in table 1, the overall cumulative incidence of any local complication after DD surgery at 30-day was 108.53 per 10,000 procedures (103.40-113.90; 1.1%) and at 90-day was 115.36 per 10,000 (110.10-120.90; 1.2%). Surprisingly, among all local complications, finger amputation was the most commonly observed one, probably because amputation will be treated as an inpatient and accurately coded in HES. The overall cumulative incidence of finger amputation at 30 days after surgery was 50.65 per 10,000 (47.19-54.37; 0.5%) and 55.49 per

10,000 (51.86-59.38; 0.6%) at 90-days. The overall cumulative incidence of finger amputation was significantly lower in primary DD surgery (Table 2) compared to reoperation surgery (Table 3) at 90-days (29.72 per 10,000 (26.83-32.92, 0.3%) vs. 146.30 per 10,000 (131.00-163.40; 1.5%)). In primary surgery, DF had the highest cumulative incidence of finger amputation at 90-days (42.48 per 10,000 (26.77-67.43; 0.4%)) followed by LF (30.28 per 10,000 (27.18-33.74; 0.3%)) and finally PNF (19.52 per 10,000 (12.85-29.64; 0.2%)). Remarkably, reoperation surgery utilising LF after primary DF carried an extremely high cumulative incidence of finger amputation at 90-day (802.10 (483.60-1331.00; 8%)). The second most common local complication following DD surgery was neurovascular injury; 39.65 per 10,000 at 30-day (36.39-42.93, 0.4%) and 40.04 per 10,000 (36.98-43.37; 0.4%) at 90-day.

Table 1: Cumulative (unadjusted) local complications within 30 and 90 days of all DD surgery (primary and reoperations) in 150,833* observations at risk

Complication	Number of events	Cumulative incidence**(95% CI)
Surgical site infection (SSI)		
30 days	51	3.38 (2.37-4.45)
90 days	59	3.91 (3.03-3.05)
Wound dehiscence (WD)		
30 days	76	5.03 (4.02-6.31)
90 days	79	5.24 (4.20-6.33)
Wound complications (SSI and WD)		
30 days	127	8.41 (6.39-10.76)
90 days	138	9.15 (7.23-9.38)
Neurovascular injury		
30 days	598	39.65 (36.39-42.93)
90 days	604	40.04 (36.98-43.37)
Tendon injury		
30 days	21	1.39 (0.91-2.14)
90 days	23	1.52 (1.01-2.29)
Finger amputation		
30 days	764	50.65 (47.19-54.37)
90 days	837	55.49 (51.86-59.38)
Any local complication		
30 days	1,637	108.53 (103.40-113.90)
90 days	1,740	115.36 (110.10-120.90)

*Denominator after excluding operations with missing sides & those with <90 days postoperative follow up=7,286/158,119 (4.6%)

**per 10,000

Table 2: Cumulative (unadjusted) incidence of finger amputation within 90 days of primary DD surgery

Operation	Number of events	Number of primary operations (N)	Cumulative incidence (95% CI)
PNF	22	11,271	19.52 (12.85-29.64)
LF	328	108,311	30.28 (27.18-33.74)
DF	18	4,237	42.48 (26.77-67.43)
Total	368	123,819	29.72 (26.83-32.92)

Table 3: Cumulative (unadjusted) incidence of finger amputation within 90 days of reoperations and their subtypes

Primary operation	Reoperation	Number of events	Number of reoperations (N)	Cumulative incidence**(95% CI)
PNF	PNF	<6*	638	47.02 (15.17-145.80)
	LF	13	1,534	84.75 (49.21-145.90)
	DF	<6*	147	68.03 (9.58-482.90)
Subtotal		17	2,319	73.31 (45.57-117.90)
LF	PNF	14	966	144.9 (85.84-244.70)
	LF	240	15,739	152.50 (134.40-173.1)
	DF	26	2,151	120.90 (82.30-177.5)
Subtotal		280	18,856	148.50 (132.10-166.90)
DF	PNF	0	21	0
	LF	15	187	802.10 (483.60-1331.00)
	DF	<6*	148	202.70 (65.38-628.50)
Subtotal		18	356	505.6 (318.60-802.50)
Overall total		315	21,531	146.30 (131.00-163.40)

**Counts of 5 or less are suppressed to prevent secondary patient identification, as per NHS Digital and ONS guidance.

**Per 10,000

4.3.1.2 Serious systemic complications

Overall, the cumulative incidence of any serious systemic complication after DD surgery was lower than that of local complications. As shown in table 4, the overall cumulative incidence of serious systemic complications was 28.69 per

10,000 procedures (26.13-31.50; 0.3%) at 30-days and 78.24 per 10,000 (73.94-82.79; 0.8%) at 90-day. All-cause mortality occurred in 3.98 per 10,000 procedures (3.10-5.11; 0.04%) at 30-days and 12.97 per 10,000 (11.29-14.91; 0.1%) after 90-days. Lower respiratory tract infection was the most commonly observed serious systemic complications, occurring in 8.15 per 10,000 (6.84-9.71; 0.08%) at 30-days and 21.71 per 10,000 (19.50-24.17; 0.2%) at 90-days. Other serious systemic complications occurred with a frequency of around 0.1% or less within 90 days of surgery.

Table 4: Cumulative unadjusted all-cause mortality and serious systemic complications within 30 and 90 days of all DD surgery (primary and reoperations) in 153,376* observations at risk

Complication	Number of events	Cumulative incidence** (95% CI)
Lower respiratory tract infection:		
30 days	125	8.15 (6.84-9.71)
90 days	333	21.71 (19.50-24.17)
Urinary tract infection:		
30 days	89	5.80 (4.71-7.14)
90 days	222	14.47 (12.70-16.51)
Myocardial infarction:		
30 days	50	3.26 (2.47-4.30)
90 days	120	7.82 (6.54-9.36)
Acute kidney injury:		
30 days	52	3.40 (2.58-4.45)
90 *days	138	9.00 (7.61-10.63)

Stroke (excluding mini-stroke) event:		
30 days	40	2.61 (1.91-3.56)
90 days	128	8.35 (7.02-9.92)
Pulmonary embolism:		
30 days	23	1.50 (1.00-2.26)
90 days	60	3.92 (3.04-5.04)
All-cause mortality:		
30 days	61	3.98 (3.10-5.11)
90 days	199	12.97 (11.29-14.91)
Any serious systemic complication:		
30 days	440	28.69 (26.13-31.50)
90 days	1200	78.24 (73.94-82.79)

*Denominator after excluding procedures with <90 days postoperative follow up=4,743/158,119 (3%)

**per 10,000

4.3.2 Self-controlled cases series (SCCS)

4.3.3 SCCS cohort characteristics

Patient characteristics in the overall cohort and in each adverse event cohort are detailed in table 5. The mean age (SD) at the time of surgery in the overall cohort was 65.5 (10.67) which is lower than in nested adverse event cohorts. The cohort of patients who suffered a UTI following surgery had the highest mean (SD) age (70.94 (10.56)) compared to other cohorts. The proportion of men was highest in the cohort of patients who suffered an MI postoperatively (87.14%) and lowest in those who suffered a UTI (71.67%). Across all nested cohorts, the proportion of

white ethnicity was very similar to the overall cohort at around 98%. Charlson comorbidity index was similar in all cohorts but slightly higher for those patients who suffered either a LRTI, stroke or AKI (median=1, IQR (1-5)). More patients in the full, LRTI and AKI cohorts were in the less and least deprived categories as compared with the more and most deprived categories. However, the majority of patients in the UTI, stroke, MI and PE cohorts were in the more and most deprived categories.

Table 5: Characteristics of patients in each cohort (full and SCCS cohorts)

Cohort	**Full cohort (n=121,488)**	**LRTI cohort (n=429)**	**UTI cohort (n=300)**	**Stroke cohort (n=180)**	**AKI cohort (n=178)**	**MI cohort (n=140)**	**PE cohort (n=67)**
Index surgery (first primary only)							
PNF, n (%)	-	58 (13.52)	31 (10.33)	24 (13.33)	26 (14.61)	19 (13.57)	<6**
LF, n (%)	-	357 (83.22)	259 (86.33)	151 (83.89)	149 (83.71)	116 (82.86)	58 (86.57)
DF, n (%)	-	14 (3.26)	10 (3.33)	<6**	<6**	<6**	<6**
Age at time of surgery, mean (SD)	65.5 (10.67)	70.31 (9.89)	70.94 (10.56)	69.89 (9.01)	70.28 (10.50)	69.98 (9.79)	68.45 (9.89)
Gender (Males), n (%)	94,458 (77.80)	355 (82.75)	215 (71.67)	151 (83.89)	145 (81.46)	122 (87.14)	50 (74.63)
Ethnicity							
White, n (%)	105,822 (98.58)	392 (98.49)	260 (97.01)	159 (100)	166 (98.81)	129 (98.47)	57 (98.28)
Others, n (%)	1,528 (1.42)	6 (1.51)	8 (2.99)	0	<6**	<6**	<6**
Missing, n (%)	14,138 (11.64)	31 (7.23)	32 (10.67)	21 (11.67)	10 (5.62)	9 (6.43)	9 (13.43)

Charlson Comorbidity Index, median (IQR)	0 (0-1)	1 (1-3)	0 (1-3)	1 (1-2)	1 (2-5)	0 (1-3)	0 (1-2)
IMD deciles, n (%)							
Least deprived 10%	13,715 (11.39)	39 (9.11)	32 (10.67)	14 (7.91)	15 (8.47)	13 (9.35)	**
Less deprived 10-20%	14,383 (11.95)	48 (11.21)	27 (9.00)	13 (7.34)	20 (11.30)	11 (7.91)	**
Less deprived 20-30%	14,764 (12.27)	47 (10.98)	23 (7.67)	18 (17.00)	17 (9.60)	8 (5.76)	6 (8.96)
Less deprived 30-40%	14,442 (12.00)	41 (9.58)	24 (8.00)	15 (8.47)	22 (12.43)	14 (10.07)	8 (11.9)
Less deprived 40-50%	13,564 (11.27)	40 (9.35)	31 (10.33)	20 (11.30)	17 (9.60)	12 (8.63)	7 (10.50)
Less and least deprived (total)	**70,868 (58.88)**	**215 (50.23)**	**137 (45.67)**	**80 (52.02)**	**91 (51.40)**	**58 (41.72)**	**27 (40.32)**
More deprived 40-50%	12,349 (10.26)	47 (10.98)	26 (8.67)	23 (12.99)	20 (11.30)	12 (8.63)	6 8.96)
More deprived 30-40%	10,958 (9.10)	45 (10.51)	34 (11.33)	22 (12.43)	14 (7.91)	17 (12.23)	7 (10.5)
More deprived 20-30%	9,686 (8.05)	41 (9.58)	38 (12.67)	20 (11.30)	16 (9.04)	15 (10.79)	9 (13.40)
More deprived 10-20%	8,520 (7.08)	50 (11.68)	39 (13.00)	17 (9.60)	23 (12.99)	20 (14.39)	10 (14.90)
Most deprived 10%	7,983 (6.63)	30 (7.01)	26 (8.67)	15 (8.47)	13 (7.34)	17 (12.23)	8 (11.90)
More and most deprived (total)	**49,496 (41.12)**	**213 (49.76)**	**163 (54.34)**	**97 (54.79)**	**86 (48.58)**	**81 (58.27)**	**40 (59.66)**

Missing	1,124 (0.93)	1 (0.23)	0	3 (1.67)	1 (0.56)	1 (0.71)	0

*Percentages for all categories were based on the total without missing as a denominator except missing category where the total was its denominator (complete case analysis)

**Counts of 5 or less are suppressed to prevent secondary patient identification, as per NHS Digital and ONS guidance.

4.3.4 Association between DD surgery and each serious systemic adverse event

Table 6 and figure 2 summarise the incidence rate ratio with 95% confidence intervals (CI) for each SCCS cohort in the 30 and 90 days postoperative periods. First primary DD surgery was associated with an increased risk of AKI by 2-fold (IRR=2.00, CI 1.14-3.53) in 30 days after surgery and by 54% (IRR=1.54, CI 1.11-2.14) 90 days after surgery. Similarly, there was an increased risk of MI by around 3-fold (IRR=2.90, CI 1.41-5.95) 30 days after surgery and by 2.5-fold (IRR=2.50, CI 1.66-3.77) 90 days after surgery. The risk of LRTI was also increased 90 days after DD surgery (IRR=1.26, CI 1.03-1.56) but there was only weak evidence for increased risk within 30 days of DD surgery. There was also weak evidence of increased risk for all other serious adverse events (UTI, stroke, PE) in both 30 and 90 day-periods after DD surgery.

Table 6: Incidence rate ratio (IRR) and 95% CI for serious systemic adverse events within 30 and 90 days of first primary DD surgery compared to each adverse event in the baseline period

Complication	Incidence rate ratio (IRR) (95% CI) for 30-day period	Incidence rate ratio (IRR) (95% CI) for 90-day period
Lower respiratory tract infection	1.18 (0.83-1.69)	1.26 (1.03-1.56)*
Urinary tract infection	1.10 (0.75-1.63)	1.24 (0.97-1.59)
Stroke (excluding mini-stroke)	0.86 (0.50-1.47)	1.21 (0.88-1.67)
Acute kidney injury	2.00 (1.14-3.53)*	1.54 (1.11-2.14)*[a]
Myocardial infarction	2.90 (1.41-5.95)*	2.50 (1.66-3.77)*

Pulmonary	1.11 (0.45-2.73)	1.51 (0.89-2.56)[b]

* p <0.05.
a: Age groups <70 were merged as group 1 and the last categories were grouped as 85+, reference category=70-74 age group.
b: Age groups <65 were merged as group 1 and the last categories were grouped as 90+, reference category was the same as other complications (65-69).

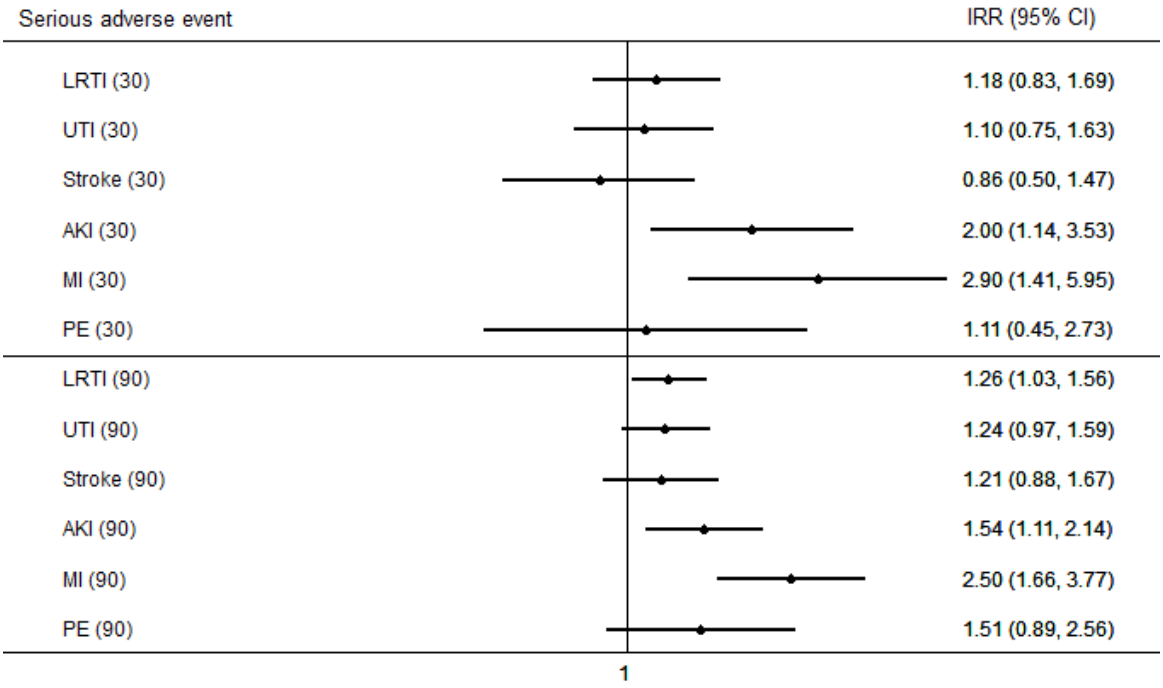


Figure 2: Forest plot of the SCCS method showing the incidence rate ratio (IRR) and 95% confidence intervals (CI) for serious systemic complications 30 and 90 days after the first primary DD surgery

4.3.5 Gender and type of surgery analysis

To examine the effect of gender on the IRR of serious systemic adverse events, this binary variable was added to the SCCS model as multiplicative interaction. Gender had no significant interaction in any adverse events except in UTI where it had a borderline significant interaction (p=0.05). To explore the exact effect of gender in UTI, stratified analysis was conducted. Male patients had a 41% increased risk of having UTI 90 days after DD surgery (IRR=1.41, CI 1.06-1.88). Females had no change in risk of UTI post-operatively (IRR=0.85, CI 0.52-1.40).

The effect of type of surgery (and thereby implied mode of anaesthesia) was examined by performing a stratified analysis as shown in table 7. First primary PNF, performed exclusively under local anaesthesia, was not associated with an increased risk of any serious systemic adverse event. First primary LF or DF surgery, usually performed under general or regional anaesthesia, was associated with an increased risk of LRTI by 30% (IRR=1.30, CI 1.03-1.63) within 90 days. AKI risk was also increased by ~ 50% (IRR=1.49, CI 1.03-2.13) 90 days within first primary LF or DF surgery. Finally, the risk of MI was increased by 2.36-fold after 30 days (IRR=2.36, CI 1.17-4.78) and by 2.24-fold after 90 days (IRR=2.24, CI 1.49-3.35) after first primary LF or DF. There was also weak evidence of increased risk for all other serious adverse events within 90 days of first primary LF or DF).

Table 7: Incidence rate ratio (IRR) and 95% CI for serious systemic adverse events within 30 and 90 days of each first primary DD surgery (PNF vs. LF or DF) compared to each adverse event in the baseline period

Complication	Type of surgery	Incidence rate ratio (IRR) (95% CI) for 30-day period	Incidence rate ratio (IRR) (95% CI) for 90-day period
Lower respiratory tract infection	PNF	0.46 (0.18-1.21)	0.89 (0.49-1.61)
	LF or DF	1.40 (0.93-2.10)	1.30 (1.03-1.63)*
Urinary tract infection	PNF	0.67 (0.11-3.99)	0.82 (0.38-1.74)
	LF or DF	1.10 (0.72-1.65)	1.28 (0.98-1.67)
Stroke (excluding mini-stroke)	PNF	4.00 (0.45-35.79)	1.30 (0.52-3.27)
	LF or DF	0.60 (0.32-1.11)	1.10 (0.78-1.57)
Acute kidney injury	PNF	1.33 (0.30-5.96)	2.02 (0.86-4.72)
	LF or DF	1.81 (0.95-3.45)	1.49 (1.03-2.13)*
Myocardial infarction	PNF	4.00 (0.45-35.79)	1.83 (0.68-4.96)
	LF or DF	2.36 (1.17-4.78)*	2.24 (1.49-3.35)*
Pulmonary embolism	PNF	**	1 (0.14-7.10)
	LF or DF	1.57 (0.61-4.05)	1.59 (0.93-2.72)

*p <0.05.
**The incidence of adverse event was to loo to allow the SCCS model to converge and give results

4.3.6 Rate of reoperations following primary DD surgery

4.3.6.1 Kaplan-Meier survival analysis

Figure 3 shows Kaplan Meier survival curve of time to first reoperation after primary DD surgery. The overall 10-year probability of not having reoperation was about 80% which corresponds to the survival probability of the first reoperation after primary LF or DF, the two most common operations, as shown in figure 4. The survival probability after primary LF or DF is similar as their curves overlap. This overlap means that primary LF and DF have the same risk of reoperation. It is noteworthy that the rate of reoperation was higher after primary PNF (~ 30%) compared to primary LF or DF (~ 20%) at the end of the study (10 years).

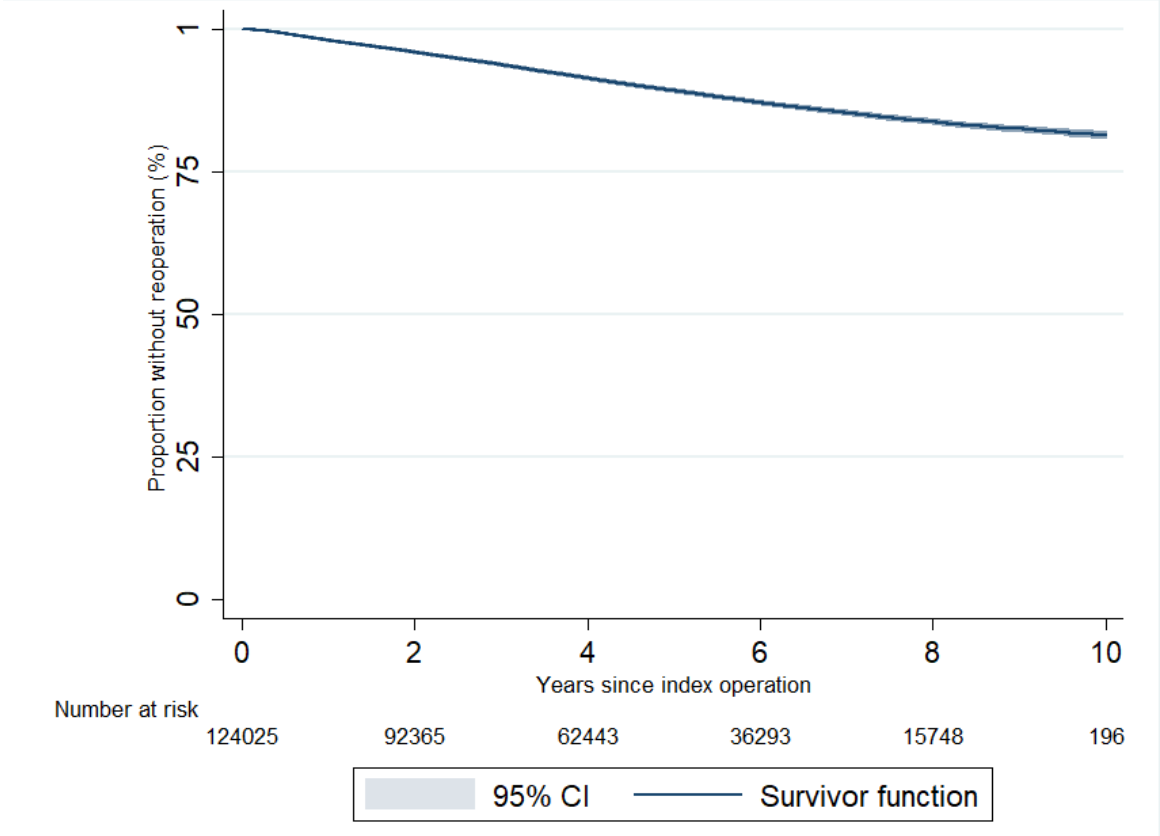


Figure 3: Kaplan-Meier survival estimate (time-to-first reoperation after primary DD surgery)

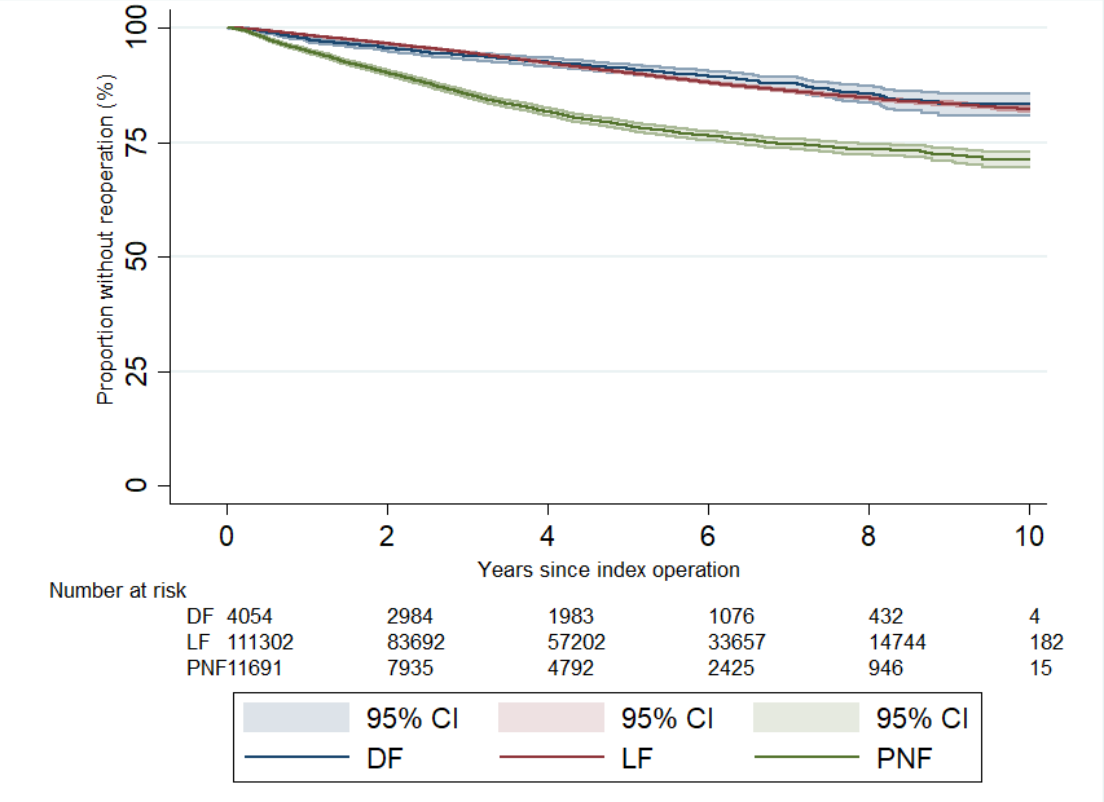


Figure 4: Kaplan-Meier survival estimate (time-to-first DD reoperation after primary PNF, LF and DF)

4.3.6.2 Cox regression analysis

Table 8 summarises the results from Cox regression analysis of time to reoperation following primary DD surgery. Higher age at time of first DD reoperation had lower risk of reoperation by 3% per year in age (HR=0.97, 097-0.97). Men had a lower risk of reoperation compared to women (HR=0.95, 0.91-0.99). Although the p value for the interaction between age and gender was significant the effect was similar between men and women (Table 9). The risk of reoperation was around 60% lower for LF and DF compared to PNF. The difference between LF and DF was not significant as their 95% CIs overlap. Lower Charlson comorbidity index was associated with a higher risk of DD reoperation e.g. a Charlson index of 0 was associated with 18% increase in risk

compared to an index of two or more (HR=1.18, 1.11-1.25). Similarly, less deprivation, as reflected by a lower IMD, was associated with higher risk of DD reoperation. For example, being in the IMD decile “least deprived 10%” was associated with increased risk of DD reoperation by 18% compared to being in the IMD decile “most deprived 10%” (HR=1.18, 1.08-1.29).

Table 8: Summary of Cox regression analysis of time-to-first reoperation after primary DD surgery

Predictor	**Hazard ratio (HR), 95% CI** for all primary DD operations**
Age at time of reoperation	0.967 (0.966-0.969)*
Gender	
Women	1(reference)
Men	0.951 (0.911-0.995)*
Type of primary surgery	
PNF	1 (reference)
LF	0.419 (0.399-0.440)*
DF	0.388 (0.346-0.434)*
Grouped Charlson comorbidity index (GCCI)	
GCCI (2 or more)	1 (reference)
GCCI (1)	1.085 (1.012-1.164)
GCCI (0)	1.175 (1.107-1.248)*
Index of multiple deprivation (IMD) deciles	
Most deprived 10%	1 (reference)
More deprived 10-20%	1.051 (0.954-1.159)
More deprived 20-30%	1.103 (1.004-1.211)*
More deprived 30-40%	1.103 (1.002-1.206)*
More deprived 40-50%	1.090 (0.995-1.192)
Less deprived 40-50%	1.135 (1.036-1.238)*
Less deprived 30-40%	1.129 (1.031-1.231)*

Less deprived 20-30%	1.188 (1.088-1.295)*
Less deprived 10-20%	1.186 (1.085-1.293)*
Least deprived 10%	1.186 (1.083-1.294)*

*p<0.05
**Rounded off to three decimal places

Table 9: Stratified analysis of age-gender interaction for Cox regression survival analysis of first DD reoperation

Gender	Hazard ratio (HR) (95% CI)	p value
Age-gender	0.996 (0.996-0.999)	0.026
Men-age	0.967 (0.965-0.968)	<0.001
Women-age	0.970 (0.967-0.974)	<0.001

4.4 Discussion

4.4.1 Local and serious systemic postoperative complications

The results of this study show that DD surgery was associated with frequent local and systemic complications after 30 and 90 days. In general, local complications had a lower overall risk (~ 1%) compared to the risks reported in the literature. For example, McFarlane *et al*[173] reported an overall risk of 17% following DD surgery. The relatively low risk in my study could be explained by a larger sample size and the fact that HES APC dataset contains details of admission episodes only; meaning that only patients with complications that were severe enough to require admission were recorded. Patients with mild complications usually present to their primary care practice and rarely to hospitals. These serious complications are still important for patients and surgeons to be aware of their

risk and to be counselled before surgery so they can make an informed decision. It's also vital for healthcare providers and policy makers because these complications add extra cost to the cost of surgery as they require admission for inpatient management.

A recent review by Dias et al[181] summarised the risk of local complications after LF, which represents the majority of the operations in my study. They found a risk of 2.9% for SSI, digital nerve injury (3.4%), vascular injury (2.1%), tendon injury (0.2%) and finger amputation (0.4%). These figures were generally higher than the ones reported in this study except finger amputation which was slightly lower than in this study (0.50% compared to 0.55%).

There is strong evidence to suggest a positive correlation between the incidence of DD postoperative complications and the severity of the initial DD deformity[181]. Therefore it's not surprising to see an increasing risk of finger amputation following primary DF and after post-DF reoperation, which is usually done for more aggressive disease. It can be hypothesised that multiple DD surgeries results in a higher risk of disruption of the vasculature of the fingers when dissecting a digital artery in a scarred bed, and therefore a higher risk of digital ischemia and amputation.

The results also show that DD surgery was associated with a relatively low overall cumulative incidence of serious systemic complications (less than 1%) as compared to one study[175] which found a cumulative incidence of 1.2%. In this small study totaling 253 patients, the authors reported three cases (0.4% each) of urinary retention, MI and congestive heart failure following LF. To my knowledge, no other previous studies have examined the incidence of systemic complications following DD surgery.

4.4.2 Self-controlled case series (SCCS) design

To my knowledge, this method has been rarely used in the literature before to evaluate postoperative adverse events except for one conference abstract evaluating risk of fracture following bariatric surgery[182]. As the mean age at time of surgery was higher in the nested SCCS cohorts, it's expected that elderly patients are more likely to have complications after surgery. Similarly, Charlson comorbidity index was higher in certain SCCS adverse event cohorts such as LRTI, stroke and AKI. The higher index in these cohorts could be explained by the fact that chronic pulmonary disease, previous stroke and chronic kidney disease are incorporated in the Charlson comorbidity index. Having baseline comorbidities at time of surgery means higher risk of exacerbation of these comorbidities or triggering new adverse events as in our cases. More deprivation (as reflected by higher IMD) in the SCCS cohorts for MI, stroke, PE and UTI cohorts which is in line with a recent report from the NHS Health Scotland[183] on the impact of living in a deprived area on health. They have found that people who live in more deprived areas are more likely to have worse health status especially cardiovascular disease and therefore be at higher risk of surgical complications. This is arguably because people who live in more deprived areas usually smoke and consume alcohol more and they are less educated about their lifestyle; therefore they have higher risk of comorbidities and complications such as cardiovascular disease. Those people with higher IMD who usually smoke and drink more have also higher risk of DD, as shown in Chapter 2. However, in Chapter 3, it was obvious that people with higher IMD have less DD surgery. Again this could indicate healthcare inequality as they have higher DD risk, less access to surgical care and higher complications after surgery.

The SCCS model allowed me to evaluate the same systemic complications using novel methodology but necessarily limited to adverse events occurring after first primary DD surgery. The results showed strong evidence for an increased relative incidence of AKI and MI within 30 and 90 days, LRTI within 90 days and UTI in men within 90 days compared to their baseline period. The relatively higher IRR of UTI in men could be explained by the higher proportion of LF and DF in men compared to women. As explained earlier LF and DF are usually performed under regional or general anaesthesia in which urinary catheterisation (known risk factor for UTI) is sometimes needed. With stratified analysis based on type of surgery, the results showed increased incidence of LRTI (90 days), AKI (90 days) and MI (30 and 90 days) following first primary LF or DF. This increased incidence could be due to the effect of regional or general anaesthesia.

4.4.3 Rate of reoperations after primary DD surgery

The results show that the 10-year rate of first reoperation after primary LF or DF was similar, and both had lower rate of reoperation after primary PNF. The rate of reoperation after PNF (30%) was comparable to the results in the literature but it was different with the regards to LF or DF reoperation rates. Foucher *et al*[184] found a reoperation (or revision – used interchangeably by the author but not clear definition) rate of 24% after primary PNF at 3.2 years follow-up. In another study, Rodrigues *et al*[185] have found a reoperation rate of 30% after primary PNF at 5 years follow-up. They have also found no statistically significant difference in the reoperation rate after LF (2.4%) compared to DF (0%) at 1-year follow-up (p=0.34) but a higher rate after LF (7.1%) compared to DF (0%) at 5 years follow-up (p=0.003). In their study, the have defined reoperation as a subsequent

surgery on the same operated finger due to disease recurrence. In a randomised clinical trial, Rijssen *et al* [80]showed a significantly higher recurrence rate following primary PNF (~85%) compared to LF (~21%) at 5 years follow-up. In another study[186], recurrence rate was 60% following PNF and 40% after LF at a median follow-up time of 4 years. The difference in the reoperation rate could be explained by difference in the reoperation definition, surgical practice or even sample size.

4.4.4 Limitations and strengths

As discussed in Chapter 2, the HES dataset is subject to misclassification bias as coding errors and inaccuracy can occur. Coding of patients' data such as diagnoses and operations is usually performed by non-medical coders, and clinicians are not usually part of the process[170]. However, the coding accuracy of routinely collected data such as HES APC has improved in the last few years as there are more financial incentives for hospitals to improve their coding to insure more accurate remuneration[96,171]. I have not specifically validated the accuracy of coding practice by checking for the coding of individual diagnoses or procedures in patient notes and therefore coding validation is recommended in future research on this topic.

Certain local complications were difficult to define or cannot be extracted from the HES APC dataset. Such complications include disease recurrence, finger stiffness and complex regional pain syndrome (CRPS). Each of these complications is important to the overall hand function for the patient.

In the literature, there is a lack of agreement on the definition of recurrence after DD surgery. A recent Delphi consensus published by Kan *et al*[187] defined

recurrence as “more than 20 degrees of contracture recurrence in any treated joint at one year post-treatment compared to six weeks post-treatment”. In HES APC dataset, degree of contracture is not reported so defining recurrence was impossible. However, the use of the term ‘reoperation’ could inform us, although not precisely, about revision surgery which may be performed in cases of recurrence. As discussed in Chapter 3, the definition of DD reoperation as any subsequent operation on the same hand has some limitations. However, it’s still clinically meaningful for both patients and clinicians.

Finger stiffness and CRPS are usually diagnosed late and difficult to capture from the HES APC data as they don’t normally require re-admission. Certain serious systemic complications were not included such as deep vein thrombosis as some patients are usually treated on outpatient basis[188]. Some other systemic complications risks such as lower respiratory tract infection (LRTI) maybe underestimated as some patients don’t have severe enough complications to require re-admission[188,189].

SCCS was limited to the first primary surgery so I couldn’t use it to evaluate secondary DD surgery (reoperation). The design of a self-controlled case series means that any fixed confounder such as gender, ethnicity are perfectly matched, and thus offers a superior design over traditional study designs such as case controls and cohort studies.

Although the study has some limitations, it has also important strengths. This study is the largest nationwide study looking at both local and systemic complications after DD surgery. As mentioned in the previous chapters, the HES APC dataset is the largest English inpatient dataset as it covers all NHS England hospitals and any private patients funded by the NHS. Serious systemic

complications were evaluated using an additional novel method (SCCS) that has not been commonly used before to evaluate adverse events after surgery. The SCCS study design has certain advantages over traditional epidemiologic studies. As SCCS method depends on comparing cases with ‘ideal’ controls, which are cases themselves, time fixed confounders are intrinsically controlled for.

4.4.5 Future work

As described in Chapter 3, it would be clinically useful to link the HES APC data extract to other real-world epidemiology datasets that contain outpatient information concerning DD patients in England such as the Clinical Practice Research Datalink (CPRD). Linking inpatient and outpatient datasets can give a broader picture of the overall complication risks, including complications that are not severe enough to require admission.

I have studied the risk of the first reoperation after primary DD surgery so estimating the risk of second and any subsequent reoperation would give a better understanding of reoperation risk.

4.5 Conclusion

In conclusion, there was a significant incidence of local and serious systemic complications following DD surgery. Some patients required further operations following their primary DD surgery and the rate of operation varied according to DD procedure type. PNF had a higher rate of first reoperation after primary DD compared to LF and DF which had similar rates. Further studies are needed to give a better understanding of DD treatment and its complications.

4.6 Chapter appendix

Table 1a: DD diagnostic (ICD v10) and operative codes (OPCS v4.4, 4.5, 4.6, 4.7) for local postoperative complications

Grouping	Condition	OPCS-4 code	Linking	ICD-10 code
Local complications	Wound complications: surgical site infection (SSI) that required wound debridement	(Z894 or Z895 or Z896 or Z897 or Z898 or Z503) + (T963 or T964 or T968 or T969)	Linked with (+)	T814 or L025
	Wound complications: wound dehiscence that required closure	(Z894 or Z895 or Z896 or Z897 or Z898 or Z503) + (S604 or S422 or S423 or S424)		
	Neurovascular injury (that required repair)	(Z894 or Z895 or Z896 or Z897 or Z898 or Z503) + (A641 or A642 or A643 or A644 or A648 or A649 or A621 or A622 or A623 or A624 or A625 or A626 or A627 or A628 or A629 and A631 or A632 or A638 or A639 or A64 or Z097)	Linked with (+)	T810 or T812
	Tendon injury (that required tendon repair)	(Z894 or Z895 or Z896 or Z897 or Z898 or Z503) + (T671 or T672 or T673 or T674 or T675 or T676 or T678 or T679)		
	Finger amputation	X082 or X083 or X084		

Table 1b: DD diagnostic (ICD v10) codes for serious systemic postoperative complications

Grouping	Condition	ICD-10 code
Serious systemic complications	Stroke (excluding mini-stroke)	I60X or I61X or I62X or I63X or I64X
	Lower respiratory tract infection (LRTI): (pneumonia, aspiration pneumonia, lung abscess with pneumonia, COPD exacerbation)	J12X or J13X or J14X or J15X or J16X or J18x J20X or J22 or J86X or J440 or J851 or J690
	Acute myocardial infarction (AMI)	I21X or I22X
	Pulmonary embolism (PE)	I26X
	Urinary tract infection (UTI)	N300 or N308 or N309 or N390 or N10
	Acute renal failure (ARF)	N170 or N171 or N172 or N178 or N179 or N990
	Death	Extracted from the Office for National Statistics (ONS) mortality data

Chapter 5. Temporal trends and geographical variation in the rate of primary Dupuytren's disease (DD) surgery in England

5.1 Introduction

Dupuytren's disease (DD) is mainly treated surgically with either percutaneous needle fasciotomy (PNF), limited fasciectomy (LF) or dermofasciectomy (DF). More recently Collagenase Clostridium Histolyticum (CCH), a non-surgical treatment option for DD, has been introduced but it is not as widely used as surgical treatment in NHS England hospitals. It is vital to understand the trend of these surgical interventions and the variation in surgical practice particularly for publicly funded healthcare systems such as the NHS. Investigating trends and regional variation in surgical practice have significant implications for the purpose of workforce planning, surgical training and improvement in healthcare delivery[190]. However, the rates of DD surgical intervention over time and its regional variation are poorly understood in the literature. A population-based study[94] using HES APC dataset evaluated temporal trends in England from 2003-2004 to 2007-2008 financial years. They found a fairly steady percentage change in all type of DD surgery between 2003-2004 and 2006-2007 financial years. However, in 2007-2008 financial year the trend changed in LF and DF likely due to a significant change in the OPCS-4 coding of DD surgery. In the US, a claims data-based study[191] showed a decline in the percentage of LF and DF and steady rate for PNF from 2007 to 2014 while CCH rose substantially from 2012 to 2014. Khan *et al*[190] evaluated inpatient databases in England (HES and other older databases) and found an increasing temporal trend for admission to plastic surgery services for all causes (near 6-fold rise from 1968 to 2004). They have

also found a significant (~5-fold) geographical variation in admission rates between 2001 and 2005

5.1 Aims:

The primary aim of this chapter was to study the temporal trends of primary DD operations in England between 2007-2018 and 2016-2017 financial years[g]. The secondary aim was to investigate the geographical variation in the rates of primary DD operations among local health geographical areas (Clinical Commissioning Groups (CCGs)) in England over the same study period.

5.2 Methods

The Hospital Episode Statistics-Admitted Patients Care (HES APC) data was used for the purpose of analysis of this chapter. DD operations (OPCS-4) and diagnostic (ICD-10) codes (detailed in Chapter 3) were used to extract episodes of DD surgery (PNF, LF, DF) from HES APC admitted from 1 April 2007 to 31 March 2017 (2007-2018 to 2016-2017 financial years).

5.2.1 Data analysis

5.2.1.1 Temporal trends analysis

Direct standardisation was used to estimate the age and gender (adjusted for year), year and gender (adjusted for age), and year (adjusted for age and gender) specific incidence of all primary DD surgery and individual surgical procedures (PNF, LF and DF). The Office for National Statistics (ONS) population

[g] Financial year in HES dataset is defined a continuous time period from 1 April of a year to 31 March of the next year.

mid-year population estimates[192] were used for each corresponding HES APC financial year as a reference population. For instance, the 2007 ONS mid-year population estimate was used a reference population for 2007-2008 HES APC financial year and so forth. The ONS population was aggregated into gender and 5-year age bands starting from age 20 and ending with age 85 and above. CCH was not included in the analysis as it is not coded in the OPCS-4 procedural codes.

5.2.1.2 Geographical variation analysis

Geographical variation was investigated at the level of Clinical Commissioning Groups (CCGs) in England. CCGs are defined as "clinically-led statutory NHS bodies responsible for the planning and commissioning of health care services for their local area"[193]. CCGs are formed of groups of smaller health areas called Lower-layer Super Output Areas (LSOAs)[194]. CCGs were established in 2012 as part of the Health and Social Care Act 2012 and replaced Primary Care Trusts (PCTs) in April 2013[195]. As of April 2019 there were 191 CCGs in England[193]. Age and gender-directly standardised rates of primary DD surgery per year were calculated for each CCG in financial years 2010-2011, 2013-2014 and 2016-2017. Rates were estimated at two levels. First, depending on the place where they received DD surgical treatment (CCG treatment). Second, based on where they lived at the time of receiving their surgery (CCG residence). A mid-year population estimate was obtained from the ONS[196] and linked with HES APC data and used as a reference population. The ONS estimate was categorised according to 5-year age bands (same bands as the temporal trend analysis), gender, year and CCG codes. CCG boundaries, as at April 2017, were obtained

from the ONS[197] to map CCG residence and CCG treatment rates. Stata MP (StataCorp. 2017. Stata Statistical Software: v15. College Station, TX: StataCorp LLC) was used to analyse the rates of DD surgery for both temporal trend and geographical analysis. The geographical information system (QGIS) software (v3.8)[198] was used to visualise the geographical variation data. Any number between 0 and 5 was suppressed to comply with the HES and ONS disclosure policies[177]

5.3 Results

5.3.1 Temporal trends

After excluding procedures with missing side code from the analysis (n=2,576; 1.6%), 127,605 (82%) of episodes were primary DD operations, and 27,938 (18%) were DD reoperations. Reoperations were further classified according to their temporal order (see Appendix - Table 1). Surgical procedures for patients aged from 18 to less than 20 were excluded (n=23) as their reference population was not available from the ONS estimates. The net total of primary DD operations included in this analysis was 127,582 operations distributed as described in table 1. The most commonly performed primary DD surgery was LF (n=11,494; 87.4%) followed by PNF (n=11,706; 9.2%) and finally DF (n=4,382; 3.4%).

Table 1: Summary table of the number and percentage of each primary DD operation in England in financial years 2007-2008 to 2016-2017*

Primary operation**	Frequency	Percent
PNF	11,706	9.18
LF	111,494	87.39
DF	4,382	3.43
Total	127,582	100

*After excluding operations with missing side (n=2,576) and age 18-20 (n=23).
**PNF: percutaneous needle fasciotomy, LF: limited fasciectomy, DF: dermofasciectomy

Table 2 summarises year specific crude (unadjusted) and adjusted rates of all primary DD operations and individual procedures per 100,000 population in England from financial year 2007-2008 to 2016-2017. The difference between crude and adjusted rate was minimal (generally less than 1 per 100,000) therefore adjusted rates were used throughout for both temporal trends and geographical analyses in this chapter. Between 2007-2008 and 2016-2017 financial years, the incidence of primary DD operations rose by 6% (from 30 (29.5-30.6) to 31.8 (31.3-32.3) per 100,000 population).

As shown in Figure 1, the highest incidence of primary DD operations in the study period was 33.4 (32.9-34) per 100,000 in 2012-2013 financial year. Primary LF followed a similar trend but the incidence decreased slightly between 2007-2008 and 2016-2017 from 27.5 (27-28.1) to 27.3 (26.9-27.8) per 100,000, a decline by 0.2 per 100.000 (0.73%). The highest peak incidence of 28.8 (28.3-29.3) per 100,000, was in 2011-2012. The incidence of primary PNF operations increased steadily from 1.8 (1.7-2) to 3.7 (3.5-3.8) per 100,000 between 2007-2008 and 2012-2013 financial years. After that, they declined to reach 2.7 (2.6-2.9) per 100,000 in 2016 and rose again to 3.4 (3.2-3.6) per 100,000 in 2016-2017; a net

increase of 89% from 2007-2008 financial year. Overall, primary DF incidence almost doubled from 0.6 (0.5-0.7) to 1.1 (1-1.2) per 100,000 between 2007-2008 and 2016-2017 financial years. From 2007-2008 to 2012-2013 financial years, the incidence rose from 0.6 (0.5-0.7) to 1.3 (1.2-1.4) per 100,000, plateaued in -2013-2014 financial year and dropped after that to reach 1.1 (1-1.2) per 100.000 in 2016-2017 financial year; a net increase of 83% in the study period.

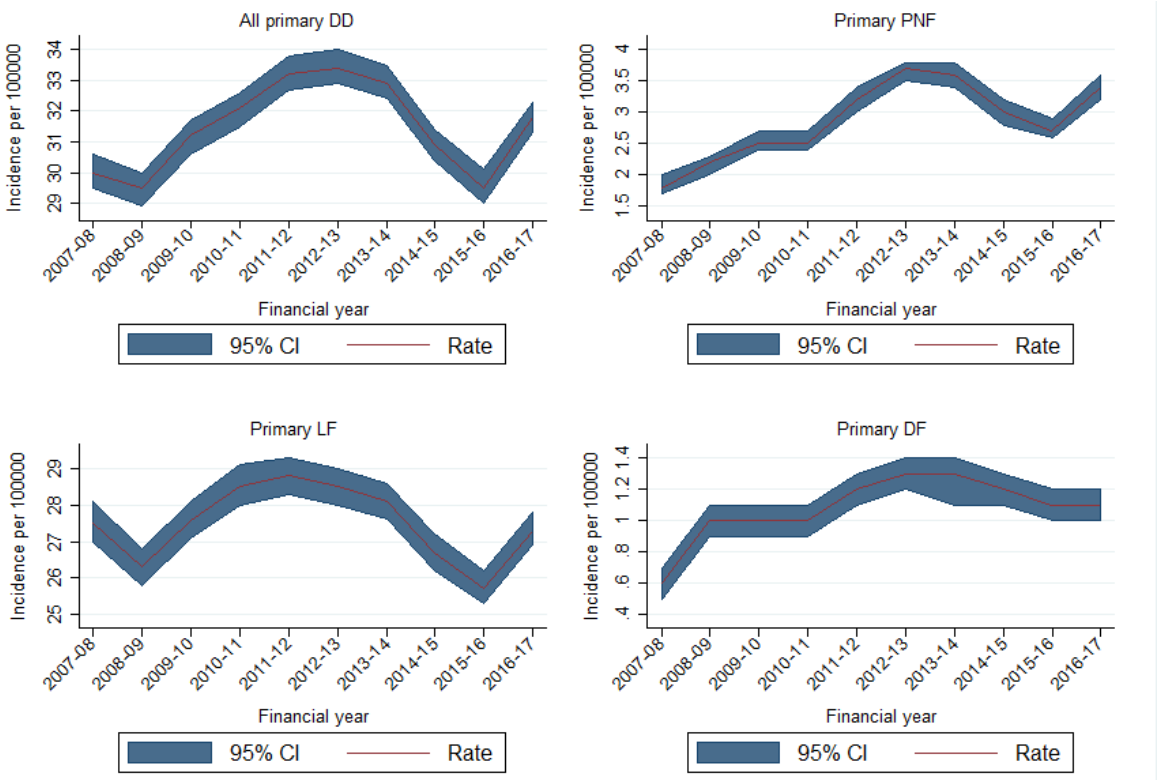


Figure 1: Year specific incidence for all primary DD operations and each individual procedure in England from 2007-2008 to 2016-2017 financial years

Figure 2 shows year and gender specific incidence for each primary DD surgery in England from financial years 2007-2008 to 2016-2017. Overall, men had more surgical operations than women for all types of primary DD surgery. For instance, in financial year 2012-2013, men had ~3.5-time higher rate of all primary DD surgery compared to women. As illustrated in Figure 3, the peak age at time of primary operation for both genders was 65-69. The incidence of primary LF

peaked at 141.2 procedures per 100,000 for the 70-74 age group, PNF at 15.6 procedures per 100,000 for 70-74 age band and DF at 5.8 procedures per 100,000 for 65-69 age group. After these peaks, in all primary DD operations, the rates dropped significantly.

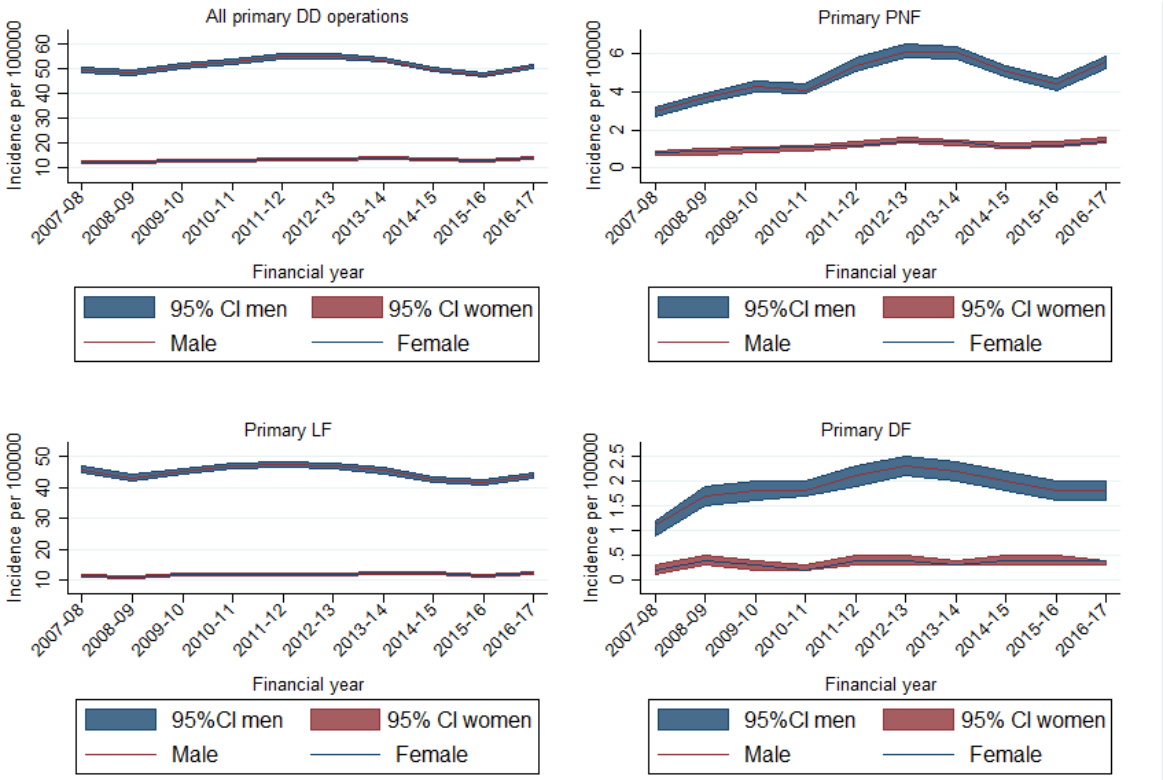


Figure 2: Year and gender specific incidence for all primary DD operations and each individual procedure in England from 2007-2008 to 2016-2017 financial years

Table 2: Summary table of year specific crude and adjusted rates of all primary DD operations and individual procedures per 100,000 population in England from 2007-2008 to 2016-2017 financial years

Financial year	ONS mid-year population	All Primary DD operations incidence (95% CI)		Primary PNF incidence (95% CI)		Primary LF incidence (95% CI)		Primary DF incidence (95% CI)	
		Crude rate	Adjusted rate	Crude rate	Adjusted rate	Crude rate	Adjusted rate	Crude rate	Adjusted rate
2007-08	38894600	29.1 (28.6-29.7)	30 (29.5-30.6)	1.8 (1.7-2)	1.8 (1.7-2)	26.7 (26.2-27.3)	27.5 (27-28.1)	0.6 (0.5-0.7)	0.6 (0.5-0.7)
2008-09	39273100	28.7 (28.1-29.2)	29.5 (28.9-30)	2.1 (1.9-2.2)	2.2 (2-2.3)	25.6 (25.1-26.1)	26.3 (25.8-26.8)	1 (0.9-1.1)	1 (0.9-1.1)
2009-10	39588900	30.6 (30-31.1)	31.2 (30.6-31.7)	2.5 (2.4-2.7)	2.5 (2.4-2.7)	27.1 (26.6-27.6)	27.6 (27.1-28.1)	1 (0.9-1.1)	1 (0.9-1.1)
2010-11	39975500	31.7 (31.1-32.2)	32.1 (31.5-32.6)	2.5 (2.4-2.7)	2.5 (2.4-2.7)	28.2 (27.9-28.8)	28.5 (28-29.1)	1 (0.9-1.1)	1 (0.9-1.1)
2011-12	40396700	32.9 (32.4-33.5)	33.2 (32.7-33.8)	3.2 (3.0-3.4)	3.2 (3.0-3.4)	28.5 (28-29)	28.8 (28.3-29.3)	1.2 (1.1-1.3)	1.2 (1.1-1.3)
2012-13	40722700	33.5 (33-34.1)	33.4 (32.9-34)	3.7 (3.5-3.8)	3.7 (3.5-3.8)	28.5 (28-29)	28.5 (28-29)	1.3 (1.2-1.4)	1.3 (1.2-1.4)
2013-14	41032500	33.3 (32.8-33.9)	32.9 (32.4-33.5)	3.6 (3.4-3.8)	3.6 (3.4-3.8)	28.4 (27.9-28.9)	28.1 (27.6-28.6)	1.3 (1.1-1.4)	1.3 (1.1-1.4)
2014-15	41409300	31.5 (31-32)	30.9 (30.4-31.4)	3.1 (2.1-3.3)	3 (2.8-3.2)	27.2 (26.7-27.7)	26.7 (26.2-27.2)	1.2 (1.1-1.3)	1.2 (1.1-1.3)
2015-16	41780700	30.3 (29.8-30.9)	29.5 (29-30.1)	2.8 (2.7-3)	2.7 (2.6-2.9)	26.4 (26-26.9)	25.7 (25.3-26.2)	1.1 (1-1.2)	1.1 (1-1.2)
2016-17	42160900	32.9 (32.4-33.4)	31.8 (31.3-32.3)	3.5 (3.3-3.7)	3.4 (3.2-3.6)	28.3 (27.9-28.8)	27.3 (26.9-27.8)	1.1 (1-1.2)	1.1 (1-1.2)

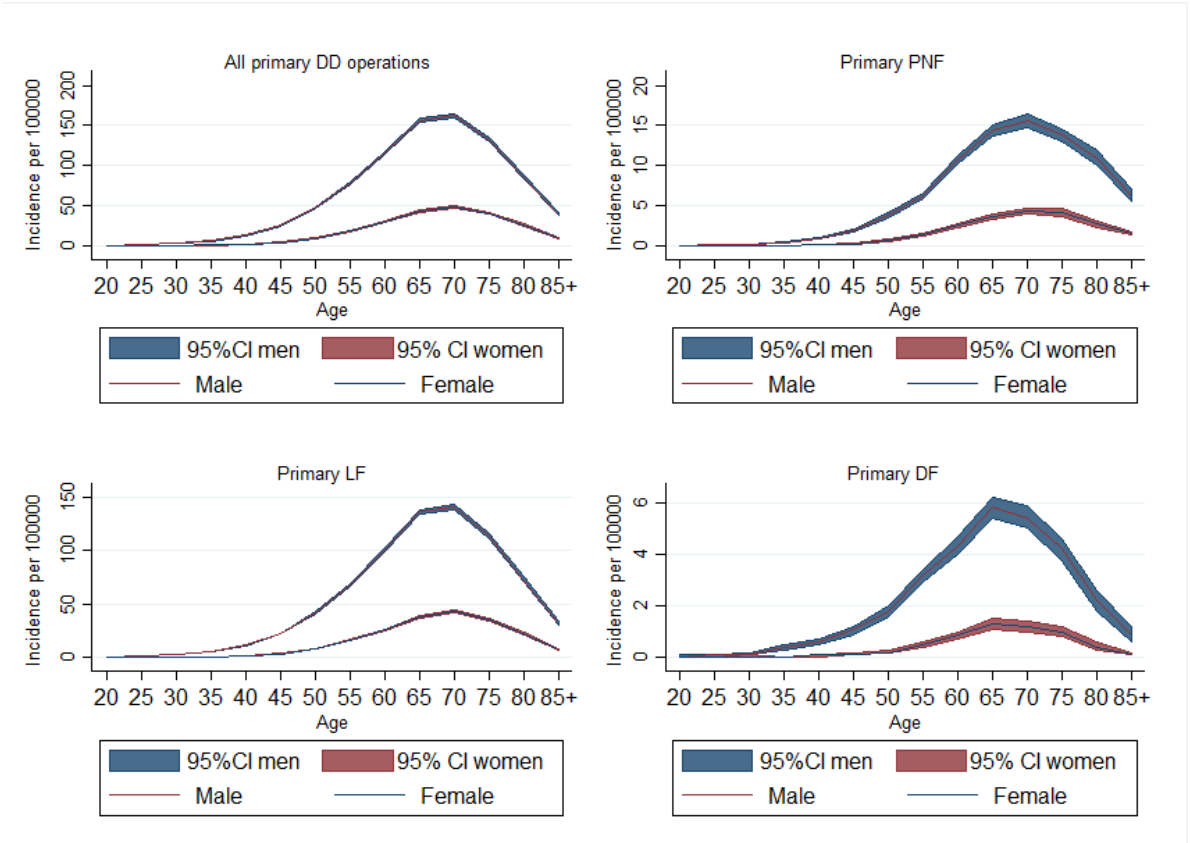
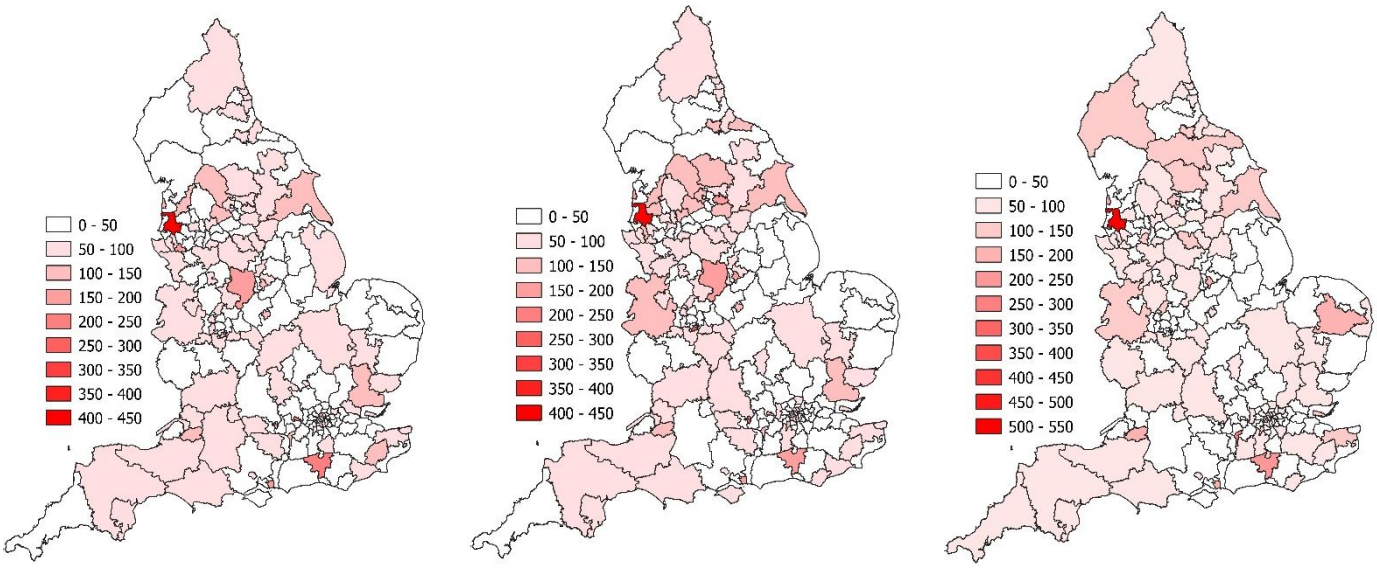


Figure 3: Age and gender specific incidence for all primary DD operations and each individual procedure in England from 2007-2008 to 2016-2017 financial years

5.3.2 Geographical variation

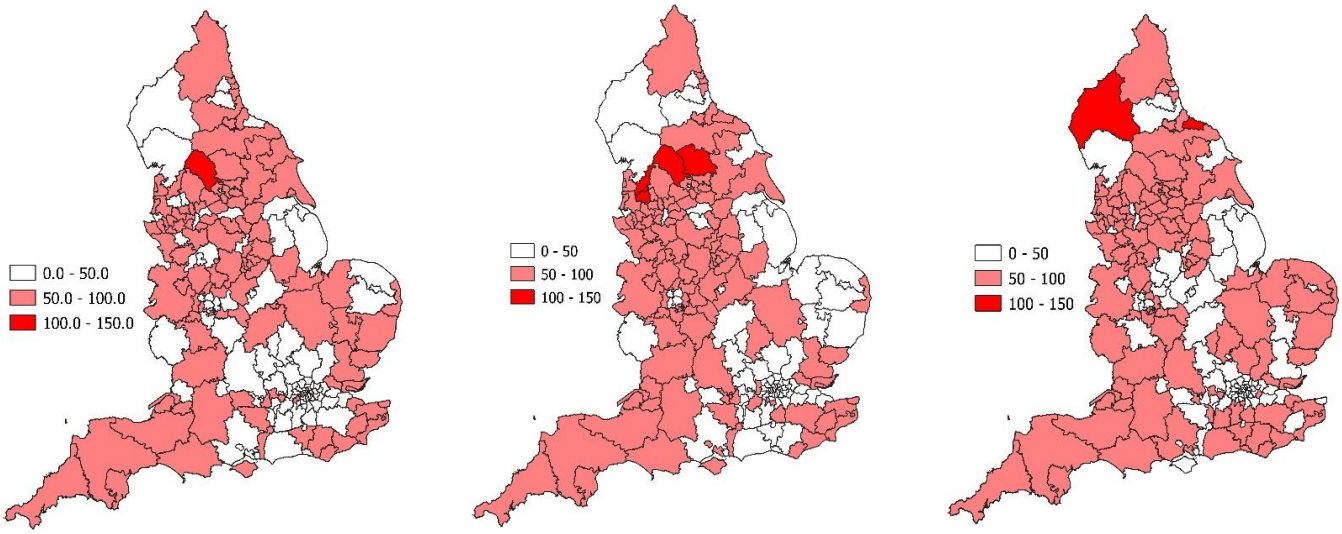
Geographical variation by CCG in the age and sex standarised rates of primary DD surgery in finaical years 2010-2011, 2013-2014 and 2016-2017 is depicted on England's map in figure 4 (CCG treatment) and figure 5 (CCG residence). These figures shows a wide variation across CCGs in terms of the rates of primary DD surgery. In financial year 2010-2011, the overall primary DD operation rates by CCG treatment varied between 1.1 (0-3.1) per 100,000 population in NHS Trafford CCG and 415.6 (362.2-468.9) per 100,000 population in NHS West Lancashire CCG and by CCG residence varied between 16.1 (5.3-27) per 100,000 poulation in NHS Barking & Dagenham CCG and 122.3 (97.2-147.4) per 100,000 population in NHS Airedale, Wharfedale and Craven CCG (Table 3). In

financial year 2013-2014, rates of primary DD operation by CCG treatment ranged from 1.7 (0-3.7) per 100,000 population in NHS West Leicestershire CCG to 434.6 (380.2-489) per 100,000 population in NHS West Lancashire CCG and by CCG residence ranged from 13.3 (3.3-23.2) per 100,000 in NHS City & Hackney CCG to 118.5 (94.3-142.7) per 100,000 in NHS Airedale, Wharfedale and Craven CCG. In financial year 2016-2017, the overall DD primary operation rates by CCG treatment varied between 0.7 (0-2.1) per 100,000 in NHS Havering CCG and 518.1 (459-577.3) per 100,000 population in NHS West Lancashire CCG and by CCG residence varied between 8.7 (1.4-15.9) in NHS Central London (Westminster) CCG and 143 (125-161) per 100,000 in NHS North Cumbria CCG. Figure 6 and 7 show the variation in rates of all primary DD operations in financial year 2016-2017 among CCGs treatment and residence respectively. In financial year 2016-2017, there was ~ 36-fold variation between lowest 10% rates (18 CCGs, 98 procedures per 100,000) and highest 10% rates (18 CCGs, 3523 procedures per 100,000) of CCG treatment rates. With regards to CCG residence variation, there was ~ 3.6-fold variation between lowest 10% rates (21 CCGs, 540 procedures per 100,000) and highest 10% (21 CCGs, 1914 procedures per 100,000) of CCG residence rates.



a. 2010-11 **b.** 2013-14 **c.** 2016-17

Figure 4: Geographical variation in age and sex-standardised rate of primary DD surgery per 100,000 population by NHS Clinical Commissioning Group (CCG) treatment in England



a. 2010-11 **b.** 2013-14 **c.** 2016-17

Figure 5: Geographical variation in age and sex-standardised rate of primary DD surgery per 100,000 population by NHS Clinical Commissioning Group (CCG) residence in England

Table 3: Age and sex standardised rates of primary DD surgery by CCG treatment and residence in three financial years (2010-2011, 2013-2014 and 2016-2017) in England

Financial year	CCG	Median	Minimum (95% CI)	CCG name	Maximum (95% CI)	CCG name
2010-11	Treatment	54.2	1.1 (0-3.1)	NHS Trafford	415.6 (362.2-468.9)	NHS West Lancashire
	Residence	52.8	16.1 (5.3-27)	NHS Barking & Dagenham	122.3 (97.2-147.4)	NHS Airedale, Wharfedale and Craven
2013-14	Treatment	53.9	1.7 (0-3.7)	NHS West Leicestershire	434.6 (380.2-489)	NHS West Lancashire
	Residence	55.3	13.3 (3.3-23.2)	NHS City and Hackney	118.5 (94.3-142.7)	NHS Airedale, Wharfedale and Craven
2016-17	Treatment	55	0.7 (0-2.1)	NHS Havering	518.1 (459-577.3)	NHS West Lancashire
	Residence	53.3	8.7 (1.4-15.9)	NHS Central London (Westminster)	143 (125-161)	NHS North Cumbria

For individual DD procedures (PNF, LF and DF) perfomed in 2016-2017 financial year, geographical variation by CCG in the age and sex standarised rates is summarised in Figure 6 and 8 (CCG treatment) and Figure 7 and 9 (CCG residence). With regards to primary PNF, the rate by CCG treatment varied between 0 and 150.7 (120.4-181) per 100,000 population and by CCG residence varied between 0 and 38.9 (23.6-54.3) per 100,000 (Table 4). For primary LF, the rate by CCG treatment varied between 0 and 355.8 (306.6-404.9) per 100,000 population and by CCG residence varied between 8.7 (1.4-15.9) and 136 (118.4-153.6) per 100,000. Finally, primary DF rates by CCG treatment varied between

0 and 82.7 (48.7-116.8) per 100,000 population and by CCG residence varied between 0 and 41.4 per 100,000.

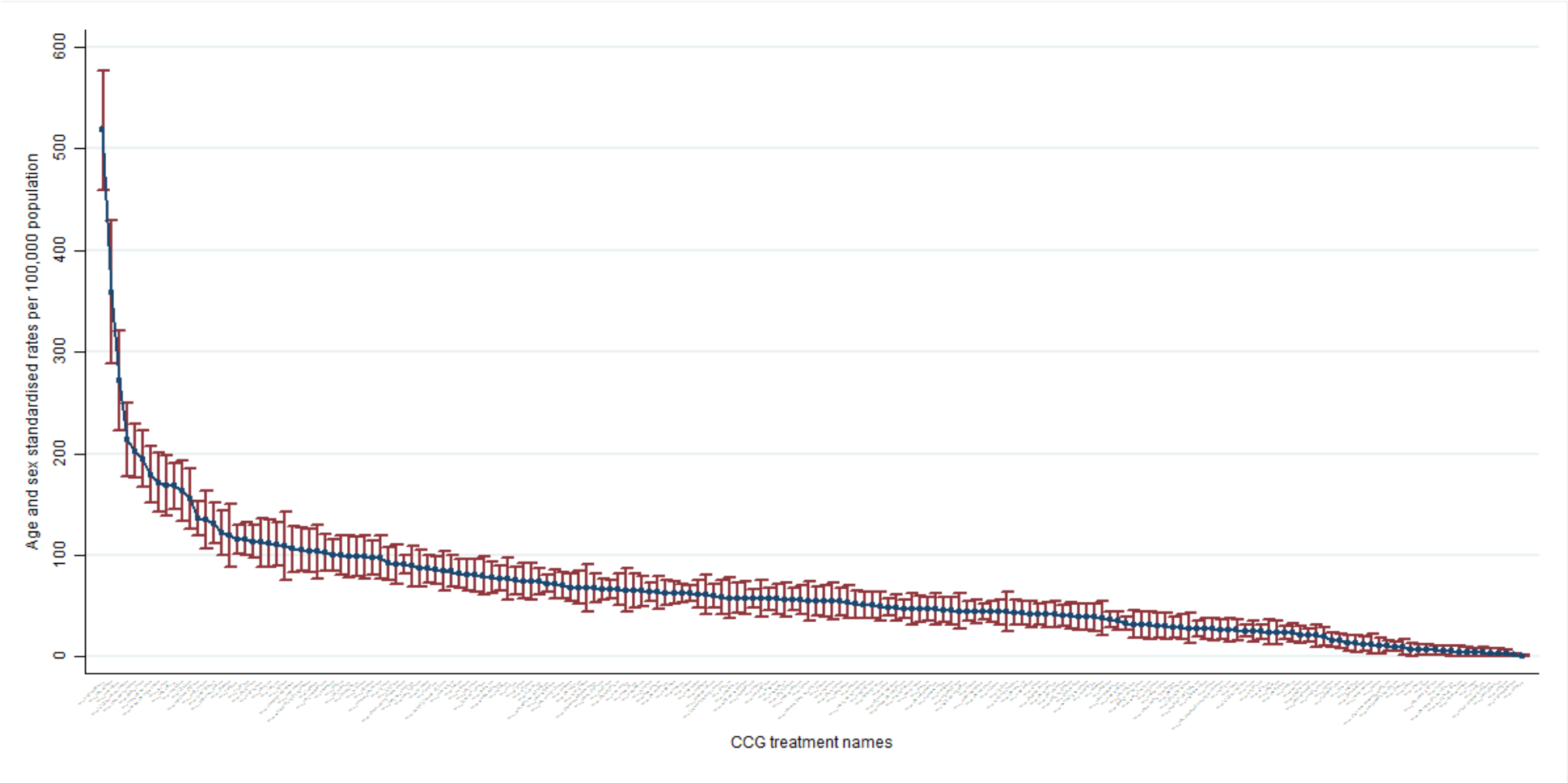


Figure 6: Summary graph of the variation in the rate (95% CI) of primary DD surgery per 100,000 population in 2016-17 by NHS Clinical Commissioning Group (CCG) treatment in England

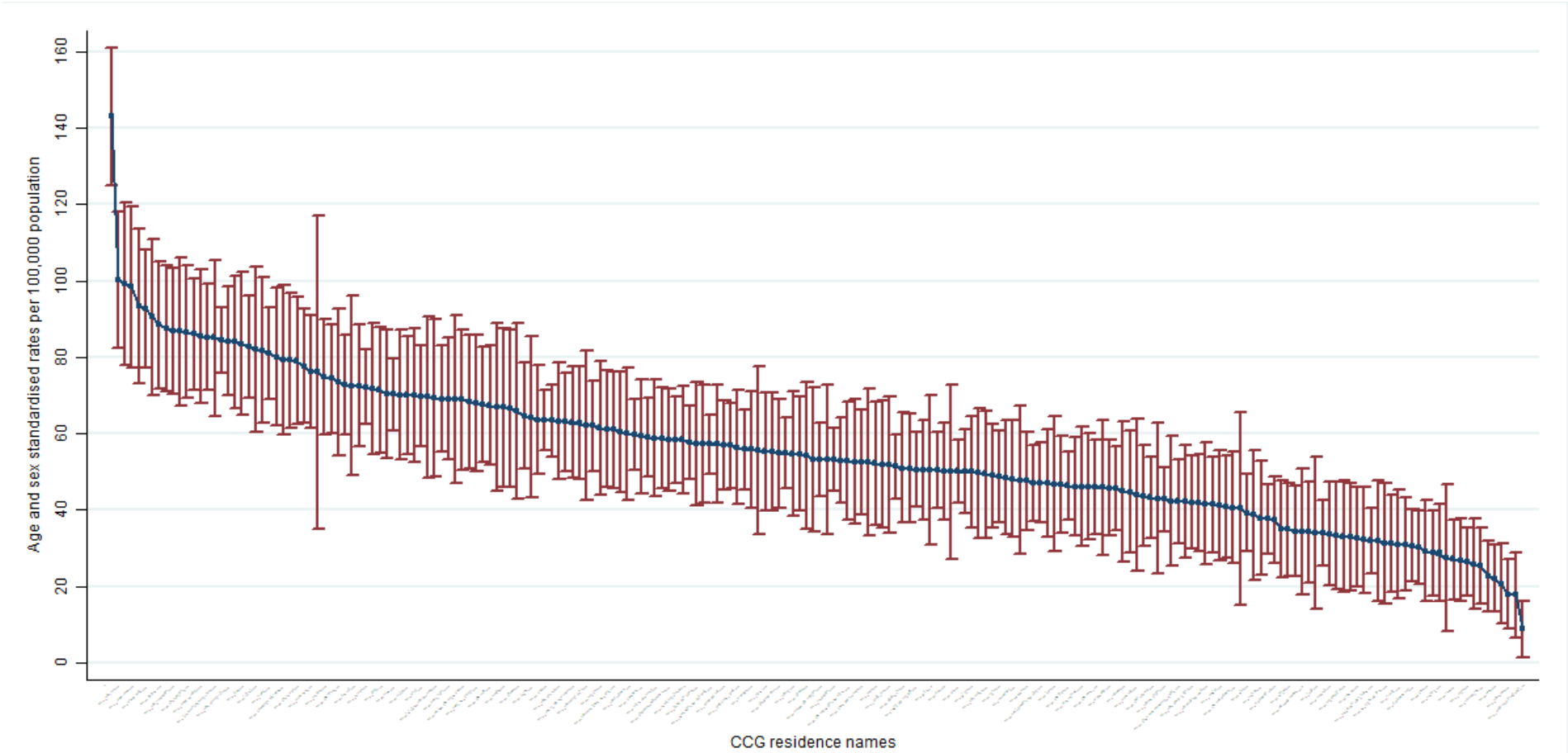
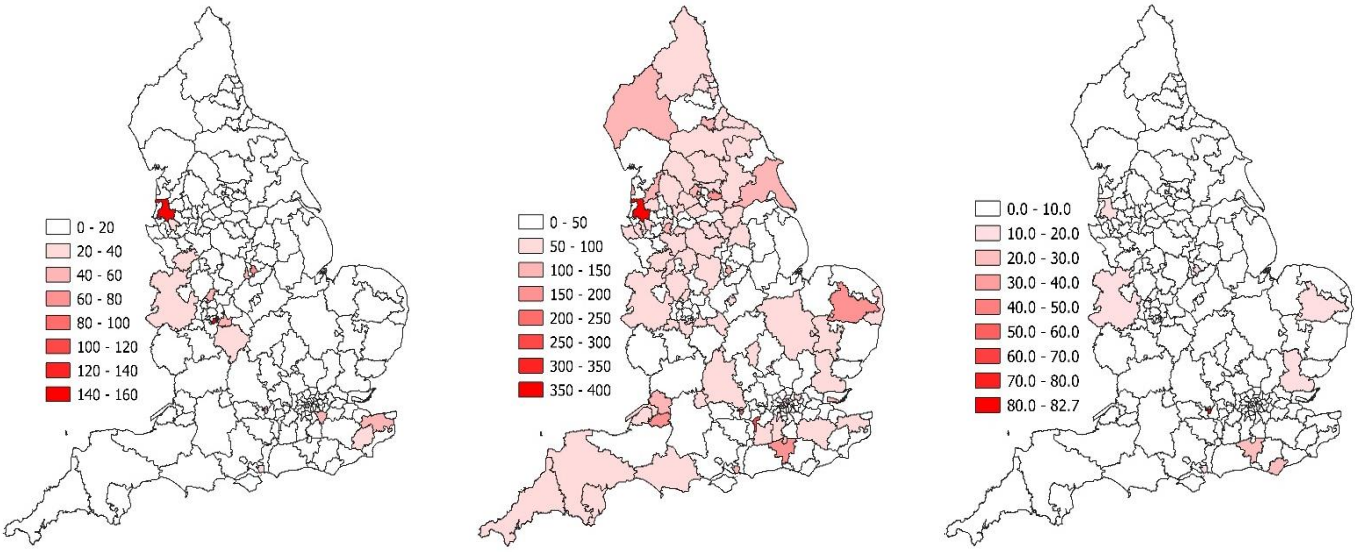
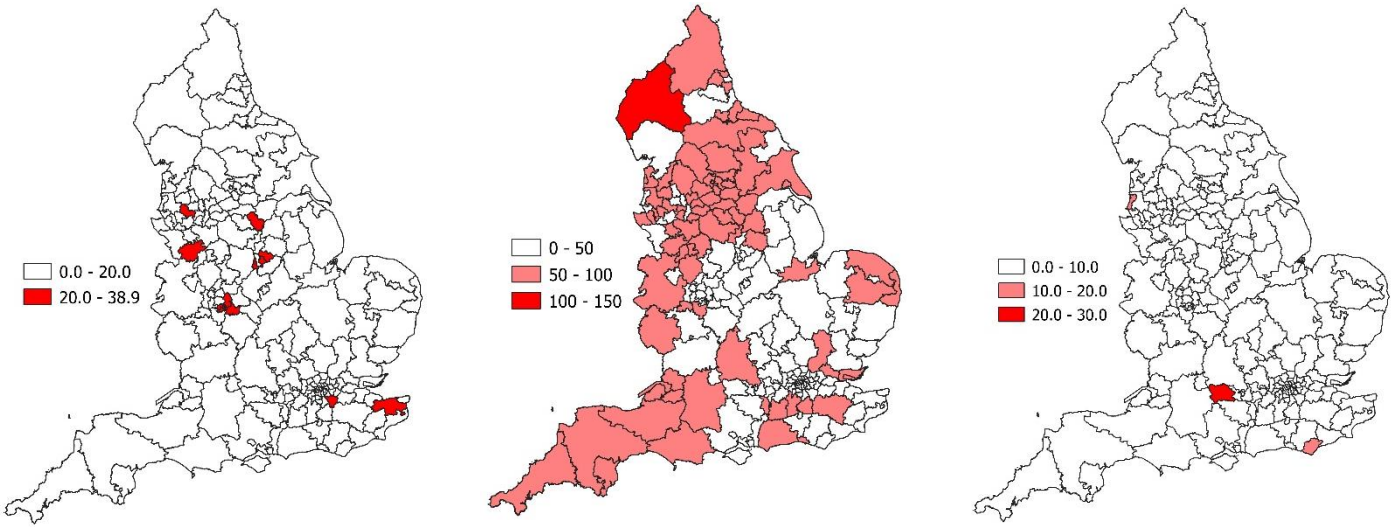


Figure 7: Summary graph of the variation in the rate (95% CI) of primary DD surgery per 100,000 population by NHS Clinical Commissioning Group (CCG) residence in England (2016-17)



a. PNF **b.** LF **c.** DF

Figure 8: Geographical variation in age and sex-standardised rate of individual primary DD procedures per 100,000 population in 2016-17 by NHS Clinical Commissioning Group (CCG) treatment in England



a. PNF **b.** LF **c.** DF

Figure 9: Geographical variation in age and sex-standardised rate of individual primary DD procedures per 100,000 population in 2016-17 by NHS Clinical Commissioning Group (CCG) residence in England

Table 4: Age and sex standardised rates of individual primary DD surgery by CCG treatment and residence 2016-2017 financial year in England

Primary DD operation	CCG	Median	Minimum** (95% CI)	Maximum (95% CI)
PNF	Treatment	2.6	0	150.7 (120.4-181)
	Residence	3.6	0	38.9 (23.6-54.3)
LF	Treatment	46.6	0	355.8 (306.6-404.9)
	Residence	45.1	8.7 (1.4-15.9)	136 (118.4-153.6)
DF	Treatment	0	0	82.7 (48.7-116.8)
	Residence	1	0	26.9 (12.4-41.4)

*Numbers less than 6 were suppressed to comply with the HES and ONS disclosure policies[11]

** In financial year 2016-2017, there were 151 CCGs treatment (PNF: 48 CCGs, LF: 1 CCG, DF: 102 CCGs) and 108 CCGs residence with no operations performed (PNF: 25, DF: 83).

5.4 Discussion

5.4.1 Temporal trends

The study results show an overall increasing trend of primary DD operation rates over the study period. The rates rose by 6% for all primary DD operations overall, which was accounted for by an increase of more than 80% for primary PNF and primary DF, but a decline by 0.7% for LF. This overall increasing trend was more pronounced in men and elderly patients in the range of 65 to 69 for all primary DD operations and DF, and a slightly older range for PNF. The rates dropped after these peaks probably because patients get older and are deemed less fit for surgery. The increasing trend could be interpreted in two ways. First, more operations are being performed due to increased prevalence of DD especially in

the ageing population therefore increased demand for surgery. Alternatively, surgeons are operating more often on patients with DD due to, for example, improved access to surgical care.

5.4.2 Geographical variation

The results show a wide variation in the rates of primary DD operations across all CCGs in England. The geographical variation was more striking with time as it reached the greatest variation in 2016-2017 financial year. This wide variation could be due to several reasons. First, variation in CCG residence rates could be explained by inequality in access to surgical care. Second, variation in CCG treatment could be due to variation surgical provision, variation in CCG funding for such surgical procedures or potentially because some CCGs do not have hand surgery units. Third, since 2013 some CCGs[199–201] have been increasingly listing DD surgery under the "Procedures of Limited Clinical Effectiveness" policy, meaning that they can only fund DD surgery if DD patients meet strict clinical criteria. Therefore, this commissioning policy may have also contributed to this wide variation. Fourth, reporting bias could be a potential cause for this geographical variation as treating centres can vary in their reporting practice and coding accuracy. Finally, variation in the prevalence of DD associations, described in Chapter 2, could lead to variation in DD prevalance and therefore variation in the incidence of DD surgery performed across CCGs. The regional variation in the rates of DD operations suggests there is a need for the development of more regulatory guidelines to standardise surgical practice across all CCGs and NHS hospitals.

In 2018, NHS England introduced a similar but a nationwide plan to save money

and regulate clinical practice[202]. It entailed restriction of funding for 17 procedures including DD surgery if surgeons do not follow a proposed clinical criteria. Although this plan has been criticised[203] as it considered DD surgery, among other procedures, as “unnecessary” or “of limited clinical effectiveness”, it arguably may help in improving consistency and elimination of unwarranted variation across CCGs in England. Future work is needed to investigate how CCGs across England changed their surgical practice particularly DD surgical management in response to the new NHS policy. More studies are required to study rates of reoperation or revision DD surgery by case volume to check whether higher case-volume hospitals and surgeons have lower complications rates as has been shown in other surgical revision procedures[204,205]. Health economics studies are also needed to evaluate the cost-effectiveness of different treatment options for DD including CCH.

5.4.3 Comparison with the literature

As discussed, there are very few studies in the literature that looked at the temporal trend or geographical variation of DD surgery. This study’s findings are in-line with a similar study[190] that used HES APC and other older inpatient databases from England. They found an increasing temporal trend for admission to plastic surgery services for any indication (near 6-fold rise from 1968 to 2004). They have also found a significant (~5-fold) geographical variation in admission rates between 2001 and 2005.

A more recent population-based study[94] using HES APC dataset evaluated temporal trends in England from 2003-2004 to 2007-2008 financial years. They found a fairly steady percentage change in PNF, LF and DF between 2003-2004

to 2006-2007 financial years. However, in 2007-2008 financial year the trend changed in LF and DF likely due to a significant change in the OPCS-4 coding of DD surgery. For example, primary surgery was separated from revision surgery and LF was further subdivided intro palmar and digital fasciectomy as discussed in Chapter 1. In my study, the findings give a more updated picture of the temporal trends and geographical variation of DD surgery that can help in understanding and improving surgical practice.

In the US, a claims data-based study[191] showed the percentage of LF and DF declined and PNF remained unchanged from 2007 to 2014 while CCH rose substantially from 2012 to 2014. They have also showed a peak age for DD surgery in 65 to 74 age group which is similar to my results. In both studies, they investigated all DD procedures (primary and reoperation or revision) and evaluated temporal trends using percentage change instead of the approach I used in my analysis (directly standardised rates) so accurate comparison with my results is difficult.

5.4.4 Limitations and strengths

It was impossible to investigate the temporal trend and regional variation of CCH as it is not coded in the OPCS-4 procedural codes. I could not also evaluate temporal trends and regional variation of DD surgery performed in private healthcare centres that do not treat patients funded by the NHS. The reason behind that is that HES dataset only covers NHS hospitals and private patients funded by the NHS. CCG data was not available before financial year 2010-2011 in HES APC so evaluation of geographical variation based on CCG was not possible before this date. Another possible limitation in evaluating rates variation

is patient migration between regions but this was addressed by analysing the rates by CCG according to place of residence and place of treatment. This study is the largest and most comprehensive study evaluating temporal trends and geographical variation of DD surgery in England. As discussed in Chapter 3, HES is subject to diagnostic and operational data coding errors and inaccuracy as the coding is usually done by non-medical coders, and clinicians are not usually part of the process [170]. Despite that, the coding accuracy of HES has improved in the last few years as there have been more financial incentives for hospitals to improve their coding to insure more accurate remuneration[96,171].

5.5 Conclusion

Over the study period (2007-2008 to 2016-2017), the results showed an overall increasing trend in the rate of primary DD surgery (all operations, primary PNF and primary DF) in England. There was striking near 36-fold and 3.6-fold variation in the rates of primary DD surgery among NHS CCGs in England according to place of treatment and place of residence respectively. Future research will be needed to study trends and geographical variation in the rates of DD reoperations, CCH injections and DD operations performed in the private sector. Cost-effectiveness studies of DD surgery are also needed to guide the development of standardised surgical practice across all CCGs and NHS hospitals.

5.6 Chapter appendix

Table 1: Summary table of the number of DD primary operations and reoperations in England in financial years 2008 to 2017

Operations	Frequency	Percent
Operations with missing hand side code	2,576	1.63*
Primary operations	127,605	82.04**
Reoperations	27,938	17.96**
1st reoperations	22,239	14.30**
2nd reoperations	4,356	2.80**
3rd reoperations	980	0.63**
4th reoperations	243	0.16**
5th reoperations	77	0.05**
6th reoperations	33	0.02**
7th reoperations	<10	0.01**
8th reoperations	<6	0.00**
Total	158,119	

*Out of total operations

**Out of total operations after excluding operations with missing side code

Chapter 6. Summary, implications and future perspective

This final chapter connects the findings presented in Chapter 1-5 and provides a brief summary of their main conclusions, implications and recommendations for future work. In this thesis I presented a narrative overview of Dupuytren's disease (DD) followed by a systematic review of the literature looking at the non-genetic risk factors for DD. I then studied DD surgical treatment epidemiology in England by analysing the Hospital Episode Statistic-Admitted Patient Care (HES APC) dataset.

Chapter 1 is an introductory chapter in which I presented an overview of DD in terms of definition, history, anatomy, pathogenesis, aetiology and clinical features. DD is a common complex fibro-proliferative disease of the palmar fascia. Previous studies reported a wide range of DD prevalence estimates and this variation could be attributed to several factors including genetic variance influencing risk; age, sex and racial composition of the population; different study sampling; varying DD classification methods and geographical variation. The mainstay of treatment of DD is surgery although non-operative treatment is described in the literature but its evidence is largely unproven or inconclusive. Finally, a description of the HES APC dataset (which was used in the analysis described in Chapter 3-5) was provided at the end of Chapter 1.

Chapter 2 is a systematic review of the non-genetic risk factors of DD. As previously discussed, DD is a complex connective tissue disorder where several genetic and non-genetic risk factors contribute in its aetiology. Despite conflicting

evidence in the literature, this review demonstrated a strong association between DD and advanced age, male gender, positive family history of DD and DM. In addition, heavy alcohol drinking, cigarette smoking and manual work exposure showed a positive dose-response relationship. This review highlighted a considerably large number of studies that reported DM as a risk factor for DD. However, more variable literature exists around other risk factors such as smoking, alcohol intake and manual work exposure. It is possible that some of these reported associations are not actually causal, but represent confounders especially in studies that did not adjust for these factors. For instance, heavy alcohol intake or smoking could be potential confounders. The evidence for the remaining factors was weak or inconclusive. Many of these associations, particularly asthma, COPD, gout, complex regional pain syndrome, malignancy, haemochromatosis, TB and HIV are likely coincidence with DD and not true risk factors. Furthermore, there was no logical reasons presented by the articles' authors for evaluating these associations in the first place.

Chapter 3 is the first HES data analysis chapter in which I summarised the characteristics of DD patients who had surgical treatme*nt in England in the study period (April 2007 to March 2017). These were demographics (age at time of surgery, gender and ethnicity), index of multiple deprivation (IMD) and Charlson Comorbidity Index. The surgical treatment pathway that DD patients followed is also described. DD surgery in England was most commonly performed in male, elderly, white patients with less financial deprivation and comorbidities. Most operations performed were primary procedures with LF being the most common type of primary surgery. Some patients required reoperation and most had a

repeat of their primary procedure. Having studied the surgical treatment of DD, it would be prudent to study DD in the overall population. The treatment pathway of DD surgical procedures can be studied further by identifying the most common pathways in patients instead of surgical operations.

Chapter 4 is the largest chapter and main focus of this thesis. It presents a detailed analysis of the incidence of local and serious systemic adverse events in the 30-day and 90-day periods after DD surgery. These complications were severe enough to require readmission for further treatment. Furthermore, it presents survival analysis of time-to-first reoperation following primary DD surgery. The results of this thesis show that Dupuytren's disease surgery performed in the NHS in England was generally safe, with a low rate of serious local and systemic complications within 30 and 90 days. However, there is high rate of amputation following re-operation, particularly limited fasciectomy following a dermofasciectomy. This requires surgeons to discuss potential risks with patients before undertaking such procedures.

We used a self-controlled case series design to ascertain that serious systemic complications including AKI, MI, LRTI, and UTI were associated with surgery for DD. In addition, these relationships persisted when analysing procedures routinely performed under general or regional anaesthesia. Patients within the nested complication cohorts were generally older, had more comorbidities, and resided in areas with higher index of deprivation. Further research should examine whether more widespread use of local anaesthesia in the surgical management of DD can reduce systemic complications.

This chapter also demonstrates that the 10-year risk of re-operation on the same hand is around 20% following either limited fasciectomy or dermofasciectomy, and around 30% following percutaneous needle fasciotomy. These data, which include all NHS England patients over a 10-year period, will allow clinicians and patients to make better informed choices regarding their personalised treatment option taking into consideration the risk of complications and reoperation following DD surgery.

Chapter 5 investigated the trends of the incidence of primary DD surgery over time and how it varied across Clinical Commissioning Groups (CCGs) in England. Over the study period, the results showed an overall increasing trend in the incidence of primary DD surgery (all operations, primary PNF and primary DF) but a slight declining trend for primary LF. This overall increasing trend requires proper workforce planning to meet the increasing demand for DD surgery. There was striking near 36-fold and 3.6-fold variation in the incidence of primary DD surgery among NHS CCGs in England according to place of treatment and place of residence respectively. This variation could reflect surgical care inequality that needs to be addressed and studied more thoroughly. Furthermore, the geographical variation could be due to variation in surgical practice, CCG funding and reporting bias. Geographical variation in the prevalence of DD risk factors, reported in Chapter 2, may result in variation in DD prevalence and DD surgical treatment.

Future perspective

Recommended future work would be to conduct meta-analysis of each studied risk factor after refining the included studies (where possible) to give more accurate summary estimate of their evidence. A further interesting investigation would be a systematic review of the genetic associations for DD development and progression. More robust prospective cohort studies e.g. using real world data such as Clinical Practice Research Datalink (CPRD) dataset and UK Biobank are needed to clarify the causal relationship of these associations with DD.

Linking HES APC database with other datasets e.g. CPRD will give a better understanding of the incidence and prevalence of DD, DD patient characterstics and DD treatment in England. Furthermore, HES APC database can be also linked to other datasets across the world such as OHDSI Collaboration (Europe) and claims datasets such as PerlDiver (USA).

The findings of this thesis can be used in the future to assist in health economics studies e.g. cost-effectiveness evaluation and economic modelling of different treatment options; both surgical and non-surgical (such as Collagenase Clostridium Histolyticum injections (CCH)).

Future research will be needed to study trends and geographical variation in the incidence of DD reoperations, and DD operations performed in the private sector. Using interrupted time series approach to evaluate the effects of the recent CCG policy of limiting the indications of DD surgery could help to confirm the temporal association and to understand health policies in NHS England. Having a more comprehensive evaluaion of the trends and geographical variation in the

incidence of DD surgery will help to guide the development of standardised surgical practice across all CCGs and NHS hospitals.

Finally, the results from this thesis can be utilised to create a real-time dashboard to help in monitoring hospital or CCG performance. This would help in improving surgical practice by providing a CCG or consultant-level feedback of DD surgical treatment in terms of complication and re-operation rates, temporal trends and regional variation.

Appendix

List of academic achievements: Since the beginning of my Master's course at Oxford (October 2018) to present

1. Scholarship, awards and grants:

-Competitive Conference Funding Scheme from Green Templeton College, University of Oxford: Grant to present my research at the Lancet Palestinian Health Alliance Conference, Amman, Jordan. March 2019

-Conference stipend from Green Templeton College, University of Oxford: Grant to present my research at the 2nd International Science Meeting for Palestine, Columbia University, New York, US. November, 2018.

-Oxford Centre for Islamic Studies Scholarship (full funding for my Master's)

2. Appointments:

-Postdoctoral research fellow, Division of Trauma, Emergency Surgery and Surgical Critical Care, Harvard Medical School, Boston, US (fully funded, starting in October 2019).

-Deputy Editor for the Science and Tech section of the Oxford Student journal; the official University of Oxford students' journal issued by the Oxford Student Union, Trinity term, 2019

-Honorary academic fellow, Oxford University Global Surgery Group

-Clinical advisor and coordinator, Oxford-Palestine (OxPal) Medlink: an educational link between medical students and doctors at University of Oxford and their counterparts in Palestine

-Research representative, Global Anaesthesia, Surgery & Obstetric Collaboration (GASOC), UK: a UK based trainee-led group made up of surgical, anaesthetic and obstetric junior doctors.

3. Publications:

-GlobalSurg Collaborative (One of the leads/collaborators for Palestine), Pooled analysis of WHO Surgical Safety Checklist use and mortality after emergency laparotomy https://onlinelibrary.wiley.com/doi/full/10.1002/bjs.11051 British Journal of Surgery (Full text)

-Alser, O., Goutos I. (2018). The evidence behind the use of platelet-rich plasma (PRP) in scar management: a literature review, Scars, Burn and Healing (Full text) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6243404/

-Alser, O., Tahboub, H., Al-Slaibi, I., Abuowda Y., Elshami M.R., Albarqouni, L. Surgical site infections following gastrointestinal surgery in Palestine: a multicentre, prospective cohort study (Abstract) https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30598-7/fulltext

-GlobalSurg Collaborative (One of the leads/collaborators for Palestine), Surgical site infection (SSI) after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study (2018), The Lancet Infectious Diseases (Full text) http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30101-4/fulltext#sec1

- Osaid Alser – From the Minarets of Gaza to the Dreaming Spires, The Oxford Student https://www.oxfordstudent.com/2019/05/01/osaid-alser-from-the-minarets-of-gaza-to-the-dreaming-spires/

4. Conferences:

-Alser, O., “Gaza Medical Students Abroad: Motives, Siege and Wars Effect, Academic Performance and Career Prospects“. The 10th Lancet Palestinian Health Alliance Conference”. Amman, Jordan. March, 2019. (Poster)

-Alser, O., “Global Surgery Collaborative Research in Palestine". The 2nd International Science Meeting for Palestine, Columbia University, New York, US. November, 2018. (Oral – invited speaker)

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