Epidemiology of Common Hand Conditions

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Abstract

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This thesis aims to appraise and analyse a variety of routine data sources to better understand their use in surgical epidemiology. The clinical focus of the thesis is to use real world data to generate a better understanding of the benefits and risks of surgery for carpal tunnel syndrome (CTS) and base of thumb osteoarthritis (BTOA) in routine clinical practice, and of the role of female hormones in the aetiology of these conditions.

A bespoke extract of administrative secondary care data (HES APC) was used to evaluate the safety of CTS and BTOA surgery and BTOA injection in routine clinical practice in England. For CTS, an observed perimenopausal peak in incidence stimulated further analysis of aetiology in later chapters. 3.42% of CTS surgeries proceeded to revision, with very low rates of serious adverse events (SAE). For BTOA, only 50% had any form of intervention after their first intraarticular injection, with 22% proceeding to surgery. Trapeziectomy was the predominant BTOA surgical subtype with an increasing trend over the 19 years studied. BTOA surgery revision intervention rate was low (1.39%), but with 2.5 times relative risk for those undergoing BTOA arthroplasty or arthrodesis compared to trapeziectomy. Very low rates of SAEs were found after BTOA intervention and prior injection did not increase post-operative complications. An extract of the UK Hand Registry was used to assess patient reported outcome following trapeziectomy versus trapeziectomy with ligament reconstruction. A significant improvement following both types of surgery was found in both general and hand specific quality of life with no difference between procedures.

In the second part of this thesis, two systematic reviews identified the role of risk factors in CTS and BTOA disease development and were used to design two studies of disease aetiology. The association of endogenous female hormones in disease aetiology was investigated using a prospective cohort (the Million Women Study) linked to HES APC. An increased risk of CTS and BTOA was associated with early menarche, an increased number of full-term pregnancies, and oophorectomy. Undergoing oophorectomy at an early age was associated with a 50% increased risk of CTS and twice the risk of incident BTOA. Finally, an international federated network analysis investigating the role of exogenous female hormonal blockade in disease development was undertaken, replicating a study designed in UK primary care data in seven datasets across four countries. This identified an increased risk of CTS and BTOA in an analysis of just under one million women who were new users of aromatase inhibitors compared to tamoxifen. A relative risk of 1.8 to two-fold for CTS in new users of AIs was seen at one year following treatment initiation, with a 40% increased risk of BTOA, revealing the same direction of effect as seen in early RCTs for AI use.

This thesis provides evidence for informed consent and shared decision making for interventions for CTD and BTOA, and provides generalisable results for use in everyday practice. It demonstrates the benefits of repurposing of data to better understand surgical disease aetiology, and illustrates how with careful curation, clinically relevant conclusions can be drawn.

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Abbreviations

AAOS American Academy of Orthopaedic Surgeons
AI Aromatase inhibitors
ASSH American Society for Surgery of the Hand
AUSCAN Australian Canadian Osteoarthritis Hand Index
AUSOM Ajou University Tertiary Hospital, South Korea
BMD Bone Mineral Density
BMI Body Mass Index
BSSH British Society for Surgery of the Hand
BTOA base of thumb osteoarthritis
CCI Charlson Comorbidity Index
CDM Common Data Model
COVID-19 Coronavirus disease 2019
CPRD Clinical Practice Research Datalink Gold
CTD carpal tunnel decompression
CTS carpal tunnel syndrome
CUIMC Columbia University Irving Medical Centre/New York Presbyterian Hospital
DOA digital osteoarthritis
DEXA dual energy X-ray absorptiometry
EQ5D index General Quality of Life patient reported outcome measure
EHDEN European Health Data and Evidence Network
EHR Electronic Healthcare Record
FESSH Federation of European Societies for Surgery of the Hand
GP General Practitioner
HES APC Hospital Episode Statistics Admitted Patient Care
HOA hand osteoarthritis
HRT hormone replacement therapy
IBM CCAE IBM Marketscan® Commercial Claims and Encounters
IBM MDCD IBM MarketScan® Multi-State Medicaid
IBM MDCR IBM MarketScan® Medicare
ICD International Classification of Disease
IFSSH International Federation of Societies for Surgery of the Hand
IMD Index of multiple deprivation
IQVIA DA France IQVIA Disease Analyzer France
IQVIA DA Germany IQVIA Disease Analyzer Germany
IQVIA HCDM IQVIA Hospital Charge DataMaster
IQVIA LPD Australia IQVIA Longitudinal Patient Data Australia
IQVIA LPD Belgium IQVIA Longitudinal Patient Data Belgium
IQVIA OC IQVIA Openclaims
IR incidence rate
JLA James Lind Alliance
JMDC- Japan Medical Data Center
LRTI Ligament Reconstruction Tendon Interposition
MCIC Minimally Clinically Important Change
MCID Minimally Clinical Important Difference
MDRR Minimum Detectable Relative Risk

NDORMS Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
NDPH Nuffield Department of Population Health
NHS National Health Service
NSAI Non-steroidal aromatase inhibitor
OCP oral contraceptive pill
ONS Office of National Statistics
OHDSI observational health data sciences and informatics
OMOP CDM observational medical outcomes partnership common data model
OPCS Office of Population Censuses and Surveys Classification of Interventions and Procedure Coding System
Optum PanTher EHR- Optum Pan-Therapeutic Electronic Health Records
Optum Clinformatics SES- Optum Clinformatics Extended Data Mart Socio-Economic Status
OUH Oxford University Hospitals NHS Foundation Trust
PEM Patient Evaluation Measure
PLE Population Level Estimation
PLP Patient Level Prediction
PROMs Patient Reported Outcome Measure
PPV Positive Predictive Value
PS Propensity Score
RCT Randomised Control Trial
SAE serious adverse events
SAI steroidal aromatase inhibitor
SIDIAP Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària
SIDIAP_H Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària linked to hospital records
SMD Standardised Mean Difference
SSI surgical site infection
STARROMOP- Stanford Medicine Research Data Repository
UKHR UK Hand Registry
UKB UK Biobank

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1. Introduction

1.1 Chapter summary

This chapter introduces the clinical and methodological aims of the thesis, and the background for choosing this focus. As an area of increasing opportunity and research interest, it appears pertinent to strategically appraise routinely collected data for its role in surgical epidemiology. Two clinical hand conditions, carpal tunnel syndrome and base of thumb osteoarthritis will be used as examples throughout the work to simultaneously generate evidence in an area where observational research is lacking. A variety of types of data are introduced for their potential in use in the study of trends in surgical treatments, outcomes following surgery, and surgical disease aetiology.

1.2 Routinely collected data in surgical research

The modernisation of medical care in a digitalised world has generated the opportunity for data generated as a by-product of routine clinical care to be used for research.[1-4] Broadly, routinely collected data, also known as real world data, can be divided by care setting, the process by which data are captured, or by the health system or population it represents.[5, 6] Examples of data generated are in the settings of primary and secondary care, of national public and insurance-based healthcare systems, regional and national populations in addition to administrative data, electronic healthcare records and condition specific registry data.

Routinely collected data enables study of large cohorts, trends over long periods of time and potential differences in response to treatment across a more heterogenous population to be evaluated. Surgical epidemiology using real world data is in its relative infancy in comparison to studies in pharmacoepidemiology.[7] In the sphere of drug licensing, the concept of post authorisation surveillance is interwoven into product development and release.[6] Observational study of surgical treatment has added layers of complexity related to surgical expertise, hospital and healthcare system factors superimposed upon device epidemiology itself. Complexity aside, it appears pertinent to develop a better understanding of how the increasing resource of routinely collected data could be used for the benefit of surgical patients, mirroring the pharmaceutical world. Providing the data generated can represent a true clinical case, using routinely collected data in evidence generation may be an efficient method of promoting research alongside clinical care as an artefact of everyday practice.

Some research questions lend themselves to observational study design. Outcomes that may be heavily associated with demographic or lifestyle risk factors for example may not be amenable to study randomised control trial, or may occur in populations often excluded from, or underrepresented in clinical trials.[8] It may not be financially viable to study in a clinical trial diseases or complications that develop over many years. These conditions are more suited to prospective cohort studies or longitudinal administrative datasets.[9] Similarly, investigation of musculoskeletal disease as a potential side effect of a treatment with established efficacy is not be ethical to submit to randomisation. For all these potential reasons- the elements of healthcare and disease pathophysiology that cannot be

randomised, the risk to the patient through exposure, and heavy financial costs- observational data may offer a role in advancing the evidence base for surgery.

1.3 Disadvantages of routinely collected data

In the context of surgical epidemiology, there are several potential disadvantages that must be considered. Firstly the procedure itself- can observational data appropriately identify the procedure, or medical device used in sufficient detail? Without accurate identification of a surgical subtype undertaken, routinely collected data may suggest incorrect associations between exposure and outcome. Secondly- can observational data truly recreate the randomised control trial, and ability to compare two very similar patients, undergoing two different procedures?[10] Whilst techniques such as multivariable adjustment for covariates and propensity score adjustment can generate very similar populations to compare surgical techniques, this can only occur if there is sufficient data for comorbidities available prior to the date of surgery in the dataset.[11] This can be difficult in some forms of real world data where there is risk from unmeasured confounding by a patient that may only enter a dataset at the point of a surgical intervention, or may transfer between healthcare providers and insurance schemes over the course of their life.[12] In addition, there may be insufficient information regarding the indication for surgery in routinely collected data, which can be a considerable source of confounding by indication. Without the knowledge of why a particular intervention was chosen by the treating surgeon, there is potential for incorrect associations with outcome to be made that actually just reflect an unidentified baseline characteristic of the patient. Finally, observational research can only ever infer or estimate causation, unlike randomised control trials.

1.4 Can routine clinical data be useful in modern orthopaedic research?

In a post-covid world it is likely that increased agility and efficiency will be required in research practice to generate meaningful evidence, especially when interactions in clinical settings may be reduced at short notice.[13] The medical environment in which this thesis was initially planned in 2017 was changed permanently by the COVID-19 pandemic, and this work reflects the dynamic nature of modern epidemiology during this timeframe. The ever-increasing generation of data as a recyclable by product of clinical interactions, the availability of cloud-based data platforms, the ability to interact within a global research community and the ability of this research to continue away from the direct clinical setting has increasing benefits in 2021.[14] With the reduction in human cost of generating real world data and the increasing availability and accessibility of data, there are benefits in the assimilation of observational studies into surgical research. Techniques can be used in observational research to emulate the study design of a randomised control trial without the cost and risk to patients through the reduction of risk of bias and confounding.[15-17] The ability to use routinely collected data also has increasing value in generating evidence for regulatory and commissioning purposes.[18] However, there also needs to be careful appraisal and evaluation of the role this data can have in orthopaedic evidence generation to prevent incorrect causal assumptions from being made.[12]

1.5 Potential areas for evidence generation

Several key areas for surgical research stand out for using routinely collected data in orthopaedic surgery.

1.5.1 Trends in surgery, risk of adverse events

Routinely collected data lends itself to the characterisation of longitudinal and temporal trends. If undertaken in a representative cohort, the estimation of rates of adverse events could generate generalisable estimates to be used in informed consent for patients. This may be particularly pertinent if different surgical techniques are undertaken for the same condition. Temporal trends can be used to identify the impact of the release of new research upon surgical practice, or the influence of a new governmental policy when studying publicly funded healthcare data. Whether this is just undertaken using one administrative data source, or a meta-analysis across many different sources, it could generate results to be used by clinicians, policy makers, regulators and governments to drive improved healthcare decisions.

1.5.2 Patient reported outcome measures (PROMS)

In a move towards a more patient centred approach to research, exploring the role of observational data could focus the definition of surgical success on patient-based metrics rather than proxies for outcome such as the incidence of complications or revision surgery. Hip and knee arthroplasty have led the way in determining the impact of surgery upon quality of life, with an increasing ability to also understand the impact of device used on outcome.[19-22] This is currently difficult in many other areas of subspecialty orthopaedic surgery, like hand surgery, due to a lack of a widely adopted high volume recording of PROMS. Research using routinely collected data in this field could identify the value of surgical intervention overall, or compare two treatment options in routine clinical practice. This would add a generalisability to results found in a randomised controlled trial setting. Use of PROMS also has the potential benefit of being used in health economic analyses to evaluate the cost effectiveness of surgery in relation to other healthcare interventions.

1.5.3 Disease aetiology

Observational study of disease aetiology enables examination of potential associated risk factors at a population level. Observational studies can explore the impact of demographic, lifestyle and socioeconomic factors as exposures of interest that can be difficult or impossible to randomise in clinical studies. The largest caveat to this work, however, is that the definition of an exposure or outcome is reliably identified in a data source and is a limitation of observational studies in comparison to RCTs. Traditionally, observational research has used medical definitions of disease as the outcome, with few studies focussed upon surgical outcomes. With a lack of observational surgical research, can we assume that the same risk factors are associated with surgically treated disease as medically treated? Is

any potential disparity between medical and surgically defined outcomes for disease due to surgical decision making and interaction with healthcare? Or does surgically defined disease represent the more severe phenotype in the spectrum of a condition? Further study of disease aetiology with surgically defined outcomes would be of benefit to the evidence base. Study of disease aetiology has traditionally been undertaken in prospective cohort studies that can provide high level evidence. The majority of these were not designed to include surveillance of orthopaedic disease incidence but could be used for orthopaedic research if they are able to be linked to routinely collected data. In this capacity, routinely collected data offers opportunity to work with allied areas of clinical research. This may enable a better understanding of how musculoskeletal disease develops, through investigating a pathological process associated with a different clinical disease subset.

1.5.4 International collaboration and federated network analyses

A common criticism of observational research is the risk of residual confounding. External validation using a different population is a method of testing the associations found but can be difficult to undertake similar analyses due data heterogeneity. During the life course of this work, a growing number of observational data networks have emerged. Some of these combine data sources into one repository, whilst others use a federated network where data remains at source.[23-26] International federated networks such as the European Health Data Evidence Network (EHDEN) and the Observational Health Data Sciences and Informatics (OHDSI) network enable studies to be replicated as precisely as possible within data that is mapped to a common data model.[27, 28] This offers the possibility of international replication in other forms of routinely collected data, to compare the potential causes of bias at a patient, surgeon, hospital, or healthcare system level.

1.6 Two selected clinical conditions

Two conditions treated by orthopaedic surgery were selected that were lacking a strong evidence base in observational research relative to other musculoskeletal areas. These conditions would be used as examples, to enable parallels to be drawn and to identify the potential for generalisability of the study design and dataset used. Through comparing the two conditions, the intention was to determine if the data source and study design could be useful in other parts of orthopaedic surgical research. The two clinical conditions chosen were Carpal Tunnel Syndrome (CTS) and Base of Thumb Osteoarthritis (BTOA).

1.6.1 Clinical presentation

BTOA and CTS are common hand conditions presenting to primary and secondary care services with an increasing prevalence. [29, 30] Both cause significant pain and reduced hand function with CTS costing over $2 billion a year in lost work in the USA. [31-33] BTOA is a term used to describe osteoarthritis of the trapeziometacarpal joint that may also be associated with arthritic changes at the scaphotrapezial joint and the scapho-trapezo-trapezoid joint. BTOA is characterised by pain and reduction in function, with debate in the literature about whether BTOA has a different aetiology to digital or interphalangeal osteoarthritis.[34-40] CTS is characterised by pain in the hand and forearm associated with paraesthesiae of the fingers caused by compression of the median nerve at the wrist.[41-43] Whilst CTS can also occur acutely following trauma, the focus of this thesis is upon chronic CTS and of defining this population from routinely collected data.[44, 45]

1.6.2 Aetiology

Traditional teaching has stated both conditions to be more common in women, based on predominantly from lower levels of evidence.[46-48] Incident CTS and BTOA are more common around menopause, with CTS and hand arthralgia frequently found during pregnancy and lactation.[48-54] There is conflicting evidence in the role of female hormones in BTOA aetiology which may reflect difference in disease definition, or the complex interplay of social and lifestyle factors.[55-60]

CTS and BTOA have both been linked to occupational exposures, autoimmune disorders, and pharmacological treatments.[42, 61-72] CTS is associated with obesity, diabetes mellitus, height, rheumatoid arthritis, hypothyroidism, gout, hand osteoarthritis, and wrist fracture, whereas BTOA is thought to be associated with osteoarthritis at other sites, wrist fracture, metabolic syndrome and rheumatoid arthritis.[67, 73-78]

1.6.3 Management

Both conditions can be treated initially with splinting, injection of corticosteroid into the scaphotrapezial joint or carpal tunnel, and surgery.[79, 80]

For BTOA, whilst steroid remains the predominant intra-articular injection for moderately severe BTOA, other substances such as hyaluronic acid and fat are suggested in the literature.[81-84] There is little clear evidence that describes the efficacy and safety of intra-articular injection, and a wide range of estimates for the risk of complications if patients progress to surgery following injection. [85-89]

The predominant surgical techniques for BTOA are trapeziectomy or trapeziectomy with ligament reconstruction and tendon interposition (LRTI), with a large variety of further reconstruction options such as arthroplasty also employed. [90-105] There is level 1 evidence that outcomes after trapeziectomy alone are equivalent to trapeziectomy with LRTI, with the latter having a higher cost and complication rate.[98, 106] Evidence for the safety and efficacy of other surgical options is based upon low level studies such as small case series.[92, 93, 106-110] Despite this clear evidence in favour of simple trapeziectomy, there remains little consensus surrounding the surgical technique employed for BTOA, with wide geographical variation, and a high risk of bias in current evidence from clinical studies.[90-105] Most of these studies compare less than 100 patients in small single centre case series, with Wajon *et al.* presenting a total of 670 patients from 11 studies in their Cochrane review of BTOA surgery in 2015.[98] There has been one previous large observational study in a sample of 5% of Medicare in the USA, but this investigated trends in US surgical practice only, identifying LRTI as the predominant surgical subtype used with no analysis of safety and no longitudinal follow up.[92] Earlier work by the same group also noted treatment choice was likely to be based upon surgeon factors.[111] Few studies to date have compared trapeziectomy or trapeziectomy with ligament reconstruction in routine practice, and very few have compared multiple surgical subtypes simultaneously. [92, 106, 109, 111, 112]

For CTS, carpal tunnel decompression (CTD) is the surgery undertaken, with this most commonly performed by an open approach in the UK.[113] Endoscopic carpal tunnel release has found favour in some countries like the USA, but remains uncommon within the NHS. A Cochrane review comparing the evidence between open and endoscopic CTD noted 28

studies comparing a variety of endoscopic and open techniques found no difference in symptom severity, functional status within three months of surgery, no difference in numbness, long term pain and no clinically meaningful difference in grip strength.[114] This systematic review also identified a high risk of bias and evidence from the 26 studies reporting complications were considered to be of low quality.

For both conditions, there is no high-level evidence of their long-term safety in routine clinical practice. Meta-analytic estimates from Vasilliadis *et al.* for carpal tunnel decompression suggested rates of 10% for minor complications such as infection, scar or pain, and 0.9% for major neurovascular or tendon injury.[114] Other studies have suggested infection rates of 0.3% and reoperation rate of 0.1% in aggregated observational and single centre studies without investigation of risk factors associated or long term reoperation rates.[115-117] Suggestions of increased risk of complications up to 35% are seen in the literature with more advanced BTOA surgical techniques such as ligament reconstruction and arthroplasty, especially if surgery is undertaken at a younger age. [97, 112, 118-120]

Whilst CTS and BTOA are thought to cause pain due to pathology originating in different anatomical structures, both conditions can present with clinical severity that does not correlate with disease severity seen in an objective test. Some studies have postulated a relationship between CTS and BTOA, and therefore studying both conditions in parallel was a logical step.[62] Two elective conditions were also chosen as I felt it was important to prevent another layer of complexity surrounding the emergency presentation of conditions associated with trauma, that would not assist in main aim of appraising the variety of routinely collected data sources for surgical epidemiological use.

There were gaps in the surgical epidemiological evidence for both CTS and BTOA that I aimed to address in my thesis. For example, only small studies of BTOA have used PROMS to focus outcome on the patient perspective.[121-124] Epidemiological studies into surgical safety have focussed upon one technique or are short in follow up. Studies of disease aetiology are focussed upon medical outcomes or have not been replicated outside of a clinical trial.[125]

The two conditions have the benefit of similarities and differences that recommend them to be used to appraise the potential value of a data source or epidemiological study design. Both conditions present to primary and secondary care, both are commonly treated with non-operative and surgical measures. BTOA has a variety of surgical techniques, including implanted medical devices, that are used to treat it, whereas CTS is treated with one main surgical technique. CTD is predominantly undertaken under local anaesthetic, whereas BTOA surgery predominantly takes place under general or regional anaesthesia. For BTOA surgery, the potential systemic complications associated with general anaesthesia can be appraised. In the UK, access to surgical treatment for the two conditions are also controlled differently in the NHS, with CTD often being restricted to certain treatment pathways and policies dependent upon the Clinical Commissioning Group (CCG), whilst BTOA surgery is unrestricted.[126] From a methodological perspective, feasibility work to define the surgeries in UK data emphasized the difference between how they are coded; CTS with 2 codes, BTOA with several hundred code combinations. This difference in coding practice also enables the two conditions to be useful in comparing the validity of surgical definitions generated for use in routine data.

This focus was also driven by the James Lind Alliance (JLA) priority setting partnership led by British Society for Surgery of the Hand (BSSH) in 2017.[127] This highlighted the need for better evidence in areas identified as important to patients, carers and clinicians that included the priority of addressing this question:

'Regarding patient and cost benefits, which interventions (for example movement preserving surgeries such as joint or cartilage replacement, fusion operations permanently stiffening the joint and novel therapies) give the best results in the treatment of painful joints in the hand/wrist?'

This thesis aims to address this JLA priority in the assessment of the role of administrative secondary care data in identifying national trends in serious adverse events following surgery, and assessing the patient reported outcomes following surgery for BTOA.

1.7 Research aims and objectives

The overall aim of this thesis is to analyse and appraise routinely collected data sources to better understand the benefits and risks of surgery for CTS and BTOA in routine clinical practice, and to develop further understanding of the role of female hormones in the aetiology of these conditions.

The aim of this work can also be subdivided into clinical and methodological aims. Clinically, I aimed to develop a greater evidence base in hand surgery, an area of orthopaedic surgery that is relatively epidemiologically naïve. Methodologically, I aimed to better understand and appraise the variety of observational data sources available to determine what can be most useful in modern surgical research practice. The work is designed to approach these

two aims simultaneously, using CTS and BTOA as the clinical focus to generate evidence, whilst using two common orthopaedic conditions as the outcomes of interest to compare the relative strengths and weaknesses of included data sources.

Initially the thesis was UK focussed. In the UK, primary and secondary care data is generated by a nationalised healthcare system bringing the added benefit of a nationally generated cohort with longitudinal follow up. For primary care, this is provided by Clinical Practice Research Datalink (CPRD); for secondary care data, this comes in the form of Hospital Episode Statistics Admitted Patient Care (HES APC). Next, I used UK based registry generated data for hand surgery (UK Hand Registry- UKHR), to appraise patient reported outcomes in a routine data source. Driven by the results from earlier chapters, I used a UK based prospective cohort (Million Women Study) linked to administrative secondary care data and studied the role of endogenous female hormones in the aetiology of surgical CTS and BTOA. Finally, I shifted to an international focus, bringing in administrative claims data from US insurance systems and electronic health records from national and regional primary and secondary care providers from Europe, Korea and the USA. I used this federated network approach to study the role of aromatase inhibitors in the two exemplar hand surgery conditions, again driven by clinical observations made on HES APC, and systematic review of the literature in earlier chapters. Whilst personal travel was prevented during the life course of this research, data was still able to travel through the use of standardised analytics. This enabled research in international datasets to continue, with the study generated in CPRD then replicated by a local data scientist Barcelona, Catalonia in Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària (SIDIAP) and subsequently in global datasets. This ability to continue research despite international restrictions due to a

pandemic was an unforeseen benefit of this programme of work, which in itself shows the potential for use of routine data in future orthopaedic research.

1.7.1 Clinical objectives

1. To estimate the incidence of primary CTD surgery and serious post-operative complications, including rates of revision surgery, in adults in the NHS in England.
2. To establish the incidence of intraarticular BTOA steroid injections undertaken in secondary care in England, the trends over time and the incidence of complications and further procedures after injection.
3. To determine the incidence of surgical subtypes undertaken in England for BTOA, the trends over time and identify the rate of revision surgery, local and systemic complications following BTOA surgery.
4. To assess if there were identifiable factors associated with progression to further intervention or complications for CTD, BTOA injection and BTOA surgery. For those undergoing preoperative BTOA injection prior to BTOA surgery, an additional aim was to identify if this was associated with an increased risk of serious surgical site infection after BTOA surgery.
5. To identify the impact of BTOA surgery upon patient reported outcome measures taken from routine UK surgical practice and to compare the change in PROMS between surgical subtypes included.
6. To systematically review the literature to identify important risk factors associated with the development of CTS and BTOA in the literature. Due to the breadth of available evidence, the CTS systematic review focused on female hormonal factors only.

Results from these chapters informed two further objectives:

7. To investigate associations between endogenous female hormonal factors (menarche, childbearing and menopause) and incident, surgically significant carpal tunnel syndrome and base of thumb osteoarthritis
8. To determine the risk of incident CTS and BTOA in post-menopausal women who are new users of tamoxifen versus new users of aromatase inhibitors.

1.7.2 Methodological objectives

1. To appraise most commonly available forms of observational data for orthopaedic research.
2. To appraise the role of administrative secondary care data available in England as a means to determining temporal trends in surgery, and in identifying patients who have a poor outcome.
3. Building upon the methodological objective 2, to test the robustness of HES APC in its ability to identify more complicated surgical procedures, surgical subgroups and treatment pathways in secondary care
4. To interrogate the UK Hand registry to determine its value in research into patient reported outcomes following surgery
5. To undertake a systematic review of aetiology to gain greater expertise in using this technique in the observational literature, including leading more junior colleagues through the blinded review process.
6. To determine if it was possible to lead and replicate an Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) designed surgical study

within the OHDSI network and undertake a federated network analysis, after initial study development and analysis in OMOP CDM mapped CPRD Gold.

1.8 Thesis Structure and content

The overall structure and content of this thesis is given in the Table 1.1.

Table 1.1 Thesis structure and content

Chapter	**Title**	**Content**
1	Introduction	Context for thesis and summary of research questions
2	Data Sources	Description of the data sources included in the thesis, their data management, validation of clinical definitions, coding, analytical methods and advantages and disadvantages
3	Administrative data HES APC: surgical epidemiology	The temporal and demographic trends in primary CTD, revision CTD and post-operative complications in HES APC. Risk factor association studies for revision surgery and complications.
4	Administrative data HES APC: surgical subtypes and treatment pathways	The temporal and demographic trends in BTOA injection, further intervention and complications for injections undertaken in secondary care are described. The temporal and demographic trends in BTOA surgical subgroups, revision surgery and complications for injections undertaken in secondary care. Risk factor association studies for revision surgery and complications.
5	Registries: UK Hand Registry	Assessment of the health state utility of surgery for BTOA, and the comparative health state utility of trapeziectomy versus trapeziectomy with ligament reconstruction.
6	Systematic review	Two systematic reviews: 1. All risk factors associated with BTOA development 2. Female hormonal factors associated with CTS development
7	Prospective Cohort Study: Million Women Study	Risk factor association study for the role of endogenous female hormonal factors in development of incident CTS and BTOA

8	Federated Network Analysis: OHDSI/EHDEN network	Pharmacoepidemiological federated network analysis of the incidence of CTS and BTOA in new users of tamoxifen versus new users of aromatase inhibitors in the treatment of post-menopausal breast cancer
9	Discussion	Summary of results, with the implications on clinical and research practice, and future directions

1.9 Associated outputs

The summary of formal presentations and peer review publications of evidence generated in this thesis are given in table 1.2, with full details of publications, including those that have been generated from the extension of this work are given below.

Table 1.2 Thesis content peer review publication and presentation

Chapter	**Podium Presentations**	**Publication status**
1		
2 Data sources	1.HES APC coding validation BSSH Sept 2016 (national)	BioRxiv 2017 and within each HES publication
3 HES CTS	1. BSSH Oct 2018 (national) 2. AAOS March 2019 (international) 3. IFSSH July 2019 (international) 4. Invited Speaker 2021 ASSH	Lancet Rheumatology Aug 2020
4 HES BTOA	Injection: BSSH Oct 2019 (national)	Injection: Rheumatology Jan 2021 Surgery: BMJ Open July 2021
5 UKHR	1. BSSH March 2018 (national) 2. Invited presentation at FESSH 2021- one of the top 10 downloaded papers of 2020 (international)	Journal Hand Surgery (European) June 2020
6 Systematic reviews		*In preparation; aim for submission July 2021*
7 MWS		*In preparation; aim for submission Sept 2021*
8 OHDSI	1. OHDSI symposium 2020 (international) 2. Invited presentation OHDSI community call March 2021 (international)	*In preparation; aim for submission August 2021*
9		

1.9.1 Publications

Serious postoperative complications and reoperation after carpal tunnel decompression surgery in England: a nationwide cohort analysis. **Lane JCE**, Craig RS, Rees JL, Gardiner MD, Green J, Prieto-Alhambra D, Furniss D.

Lancet Rheumatology 2020 Sep 30;3(1):e49-e57. PMID: 33381769

Low rate of subsequent surgery and serious complications following intra-articular steroid injection for base of thumb osteoarthritis: national cohort analysis. **Lane JCE,** Craig RS, Rees JL, Gardiner MD, Shaw AV, Spiteri M, Kuo R, Dean BF, Green J, Prieto-Alhambra D, Furniss D. *Rheumatology.* 2021 Jan 7;keaa925.PMID: 33410485

Low rates of serious complications and further procedures following surgery for base of thumb osteoarthritis: analysis of a national cohort of 43 076 surgeries.

Lane JCE Craig R, Rees JL, Gardiner M, Mikhail MM, Riley ND, Prieto-Alhambra D, Furniss D. *BMJ Open*. 2021;11:e045614 doi:10.1136/bmjopen-2020-045614

Basal thumb osteoarthritis surgery improves health state utility irrespective of technique: a study of UK Hand Registry data. **Lane JCE**, Rodrigues JN, Furniss D, Burn E, Poulter R, Gardiner MD.*J Hand Surg Eur Vol.* 2020 Jun;45(5):436-442. PMID 32162998

1.8.1.1 Associated publications from extension of work and collaboration

Serious adverse events and lifetime risk of reoperation after elective shoulder replacement: population based cohort study using hospital episode statistics for England.

Craig RS, **Lane JCE**, Carr AJ, Furniss D, Collins GS, Rees JL. *BMJ* 2019. Feb 20;364:l298. PMID: 30786996

Risk factors for progression of finger interphalangeal joint osteoarthritis: a systematic review. Shah K, Yang X, **Lane JCE**, Collins GS, Arden NK Furniss D, Filbay SR. *Rheumatol int.*2020 Aug 24. PMID: 32839851

Serious complications and risk of re-operation after Dupuytren's disease surgery: a population-based cohort study of 121,488 patients in England. Alser O, Craig RS, **Lane JCE,** Prats-Uribe A, Robinson DR, Rees JL, Prieto-Alhambra D, Furniss D. *Scientific Reports* 2020 Oct(5);10(1):16520. PMID: 33020582

Management of osteoarthritis at the base of the thumb. Parker S, Riley N, Dean B; **Oxford Upper Limb Collaborative**.*Bone Joint J.* 2020 May;102-B(5):600-605.PMID: 32349588

Prognostic factors for finger interphalangeal joint osteoarthritis: a systematic review. Shah K, Cai H, **Lane JCE,** Collin GS, Arden NK, Furniss D, Filbay SR. *Rheumatology* 2021 Mar 2. 60(3):1080-1090 PMID: 33253392

Temporal trends and geographical variation in Dupuytren Disease surgery in England. A population based cohort study. Alser O, Abram SGF, Craig RS, Lane JCE, Shaw AV, Prats-

Uribe A, Rees JL, Prieto-Alhambra D, Furniss D. *Ann Plast Surg* 2021 Sep 1;87(3):265-270.

PMID: 34397515

2. Data Sources

Contributions: All work in this chapter was designed, conducted and analysed by myself apart from assistance with validation studies in the datasets. In section 4.3.2.1 Mr Wee Leon Lam and Dr Lucy Popplewell assisted as second reviewers of patient notes with the data extract generated by Dr Christian Schnier in UK Biobank and senior advice from Prof Cathy Sudlow; Mr Akira Wiberg assisted as the second reviewer of patient notes with data extract for the validation study generated by Dr Angela Balkwill and Dr Kirstin Pirie for MWS. In section 4.3.2.2.1 Miss Michelle Spiteri, Miss Abigail Shaw and Mr Ben Dean assisted as reviewers of patients notes, and in section 4.3.2.2.2 Mr Nicholas Riley and Mr Mark Mikhail assisted as reviewers of patients notes. In section 2.5.6 for Cohort Diagnostics in OHDSI whilst I designed wrote and ran the analytical package in CPRD, the analytical package I developed was run in these datasets with thanks to the following collaborators:

Source	Collaborator
AUSOM	Dr Seojeong Shin, Dr Seng Chan You
CIUMC	Dr Thomas Falconer
IBM CCAE, IBM MDCD, IBM MDCR, IQVIA LPD Australia, IQVIA DA France, IQVIA DA Germany, JMDC, Optum PanTher EHR, Optum Clinformatics SES, Pharmetrics	Mr Josh Ide, Mr Alan Andryc, Mr Stephen Fortin
IQVIA Hospital Chargemaster, IQVIA LPD Belgium, IQVIA Openclaims	Mrs Kristin Kostka
SIDIAP, SIDIAP_H	Dr Edward Burn
STARROMOP	Dr Jose Posada

Assimilation and aggregation of all data into shiny application was undertaken by myself.

2.1. Summary

This chapter introduces the data sources included in this thesis, addressing the main methodological aim of appraising available observational data for orthopaedic research. This chapter highlights the variety of possible real-world data used and aims to robustly identify the strengths and weaknesses that UK and international data sources have to offer. The intention was that through using a variety of data sources, one dataset can attempt to address the criticisms and weaknesses of another. This chapter follows the temporal path of discovery in the work from secondary care in England and the UK hand registry, to using the Million Women Study prospective cohort study linked to secondary care data and using UK primary care data within an international federated network of observational data mapped to a common data model.

2.2 HES APC: Routinely collected data in secondary care in NHS, England (chapters 3 & 4)

The first dataset to be interrogated, Hospital Episode Statistics Admitted Patient Care (HES APC) is a secondary care based administrative data that has the huge advantage of long longitudinal follow up and coverage of all NHS admitted patient care services in England.[128] However, it also brings the disadvantage of selection bias and coding error due to its generation as a by-product of remuneration of NHS services.

2.2.1 Setting

HES APC contains all remunerated NHS admitted patient care, including that undertaken by independent providers who undertake procedures on behalf of the NHS. This can be a day

case episode or longer but will only register as an episode of care if it includes some form of admission. It contains basic demographic information including socioeconomic deprivation data in the Index of Multiple Deprivation (IMD), ethnicity and age.[129] It provides the diagnoses and procedures undertaken during the admission alongside dates and hospital provider, in addition to the registered GP practice. This extract contains some pseudonymised elements to prevent secondary disclosure of data, including month and year of birth rather than full date of birth, the first half of the patient's home postcode and pseudonymised clinician provider codes to prevent individual consultant physician/GP identification.

A bespoke extract of individual patient data (01/04/1998-31/03/2017) was provided by NHS digital for all patients who were identified as undergoing an intervention of interest (Appendix tables A.1 and A.2). This was made by extraction from the main year files held by NHS digital, using a given code list generated by the validation study described below. After identifying the patient with the outcome of interest, all other incident and prevalent admitted patient episodes of care that were remunerated by the NHS were also extracted by NHS Digital through linkage by an individual NHS number and collated into the extract. The linkage of all episodes of care for a patient through their individual NHS number enables identification of care episodes that occur in any secondary care provider within the NHS in England, and therefore can identify complications or revision procedures undertaken outside of the hospital where the index procedure took place. It is estimated that only 11% of the UK population hold private health insurance and 13% of surgery is undertaken privately, therefore indicating that the NHS workload represents the vast majority of secondary care undertaken which would be represented in HES APC.[130] By design, this raw

individual patient level data was collected by NHS Digital and linked to Office of National Statistics mortality data, with all data pseudonymised prior to being released for research.[131] Details of the processing undertaken to make a research ready flat file (i.e. inclusion, exclusion criteria, diagnosis and procedure fields used) from the originally released data are given in section 2.2.6.

2.2.2 Data collection

Up to 20 diagnoses and up to 24 procedures are recorded per episode in HES APC.
For each study, a smaller dataset was generated for the condition of interest using a validated list of procedure and diagnosis codes. Procedures are classified in HES APC using the Office of Population Censuses and Surveys Classification of Interventions and Procedure version 4.8 (OPCS-4.8) coding system and disease diagnosis classified using the International Classification of Disease version 10 (ICD-10) codes (Appendix A tables A.1 and A.2).[132, 133]

These condition specific datasets were designed to include elective surgical cases only for both BTOA and CTS, and therefore excluded patients who had a diagnosis code for a fracture in the same episode of care to prevent inclusion of cases associated with trauma. The OPCS and ICD code combinations were tested to determine if they were fit for purpose prior to any analysis being undertaken through validation studies.

2.2.3 Data Quality- Validation studies

Co-authors: Christian Schnier, Cathy Sudlow, Wee Leon Lam and Lucy Popplewell (UK Biobank); Jane Green Angela Balkwill, Kirstin Pirie and Akira Wiberg (MWS)

Two types of validation study were undertaken to determine if UK routinely collected data could be reliably used to identify cases of surgically treated CTS and BTOA. Firstly, an internal validation study was undertaken to determine if the two conditions could be identified at all and to calculate the positive predictive value (PPV) of the proposed OPCS and ICD code lists. Secondly, further validation studies were undertaken to determine if BTOA surgical subtypes and the BTOA injections could be identified within the BTOA cohort.

2.2.3.1 Main validation study- methodology

A list of OPCS procedure and ICD diagnosis codes was generated through multidisciplinary iterative discussion between surgeons, clinical coders, epidemiologists and NHS Digital. In addition, a list of READ codes for use in primary care dataset Clinical Practice Research Datalink (CPRD) was also generated. This work was undertaken in partnership with UK Biobank in order to develop a sample of patients for the validation study, with healthcare records appraised in Edinburgh and Oxford.

UK Biobank participants with the relevant codes in their associated routinely collected healthcare data were identified and anonymised. Two clinicians then reviewed their electronic healthcare records, which for those in Scotland, was linked to their primary care record. Algorithms were generated *a priori* by the multidisciplinary team to determine the definition of a true disease case (Appendix A Figures A.1 and A.2). Inter observer reliability was then determined between the two clinicians. This was subsequently replicated in Oxford through identification of participants within the Million Women Study (MWS) who

were identified by the code definitions in their associated routinely collected healthcare data. In Oxford, only secondary care healthcare records were interrogated. Results of these studies are described in Chapters 3 and 4 alongside the analysis of HES APC for CTS and BTOA respectively.

2.2.3.2 Limitations

This work was carried out in collaboration with two prospective cohort studies and investigated electronic healthcare records from two teaching hospitals. A limitation is that UK Biobank (UKB) records were based in Scotland using the same coding system as is used in HES APC, but this is likely to represent the PPV for HES APC, especially as results were replicated in Oxford using participants of MWS that is linked to English HES APC. One criticism suggested when this work was presented at the BSSH national conference is that this also represents two affluent areas of the UK and two teaching hospitals, where coding practice may be more accurate. Further work could be undertaken to address this in a district general hospital setting outside of these two regions to externally validate the generated code list.

2.2.3.3 Validation: BTOA subgroups- methodology

Following the initial validation study, two further studies were run locally in Oxford University Hospitals NHS Foundation trust to identify if HES APC could identify BTOA intra-articular injections and surgical subtypes undertaken for BTOA. This was a study specifically for BTOA since surgically treated CTS does not present a large variety of surgical subtypes as is seen with BTOA. Whilst endoscopic CTD can be undertaken, this remains rare in UK

practice and would not represent a typical cohort of patients in NHS care. Again, an iterative multidisciplinary process was followed to generate a list of codes to identify BTOA intra-articular injections and BTOA surgical subtypes. For both BTOA injection and BTOA surgical subtypes, a year cohort of patients were identified from electronic health records, and their records independently appraised by two clinicians to determine the PPV of the code list generated. Results generated are discussed in detail in Chapter 4.

2.2.3.4 BTOA subgroups- limitations

These validation studies were undertaken to give a better understanding of routine NHS coding practice at a more granular level than was possible in the initial UKB/MWS led validation study.

2.2.4 Data Analysis-missing data

In all three cohorts (CTD, BTOA injection, BTOA surgery), missing data for baseline demographics (age, sex, ethnicity and IMD) was low. In the CTD analysis, incomplete records represented 0.72% of the cohort; for BTOA injection 0.74%, and BTOA surgery 0.95%. This data appeared to be missing at random, and therefore as this level of missing baseline was also low, no imputation was employed with the HES APC studies.

2.2.5 Data processing

Data was released in raw year files from NHS Digital and processed into a usable format using STATA 15. All data was processed and analysed within the secure data room in the

Botnar research centre. Episodes of care under each new consultant clinician were released as independent events, and therefore data was processed to generate finished consultant episodes (FCEs) combining all elements of one hospital admission into a cohesive spell. Multiple episodes were gathered into date order using the pseudonymised HES identifier (HESID) to generate prevalent and incident episodes around the index procedure. Duplicated episodes, especially those frequently occurring over financial year ends were also removed as necessary. Charlson Comorbidity Index (CCI), a measure of overall comorbidity was generated using the STATA using *charlson* function, and ethnicity defined in the standard groups as given by NHS Digital.[134, 135] IMD remained used as deciles where possible to maintain granularity of analysis or combined into quintiles to enable multivariable logistic regression analysis where case numbers were small. Data was then processed to generate one row per patient. Further methodology surrounding the identification of primary surgeries, the linkage of laterality and identification of complications and revision interventions for CTS and BTOA procedures are given in chapters 3 and 4.

2.2.6 Advantages and Disadvantages

HES APC has the benefit of being generalisable to a national population undergoing intervention in a nationalised health system. There is no limit upon age of included patients, and no regional restriction for inclusion. All remunerated activity will be present within HES APC, giving the benefit of also including private providers undertaking NHS work. This suggests that serious adverse events that are expensive healthcare encounters will more likely be included in the dataset and may in fact represent the upper estimates of risk. The

ability to longitudinally capture patient activity within a nationalised health system is of significant benefit compared to administrative data generated in privatised healthcare, where patients can enter and exit within short periods of time based upon insurance or interaction with the system. Outside of Scandinavia very few countries have observational data sources that enable the longitudinal follow up possible within HES. The ability to identify a patient presenting to another hospital is also beneficial, enabling complications or revision surgery undertaken by other providers to still be included which may occur if patients are dissatisfied with their care at the original centre. This highlights the significant disadvantage of using an electronic healthcare record system based within only one hospital trust compared to HES APC.

This data is limited to representing England only and does not include the devolved nations. As it was not designed for a research purpose and therefore will contain the inclusion and selection biases due to coding practices driven by remuneration. Similarly, it will not include diagnoses that do not require admission or are treated within the emergency department or outpatient clinic and therefore studies based in primary and intermediate care will be needed to identify complications that would be treated in these areas. There is little information for the non-operative management undertaken or for potential confounders such as occupation and lifestyle factors. There may be a bias towards the inclusion of diagnoses and procedures that carry higher remuneration such as obesity, with other comorbidities being missed out. When determining past medical history using HES APC, one can only detect any comorbidities that are included in a prior or the current episode of care. This may cause the comorbidities to only be identified in patients with the most severe

forms of the disease, and cause patients treated for a condition in primary care to be considered disease free.

2.2.7 Approval

All work in HES APC was approved by the NHS Data Access Advisory Group (DAAG) and NHS Digital Data Sharing Agreement (DARS-NIC-29827-Q8Z7Q). The programme of work was registered at clinicaltrials.gov (NCT03573765). As the study did not use identifiable data, it was considered exempt from research ethics committee approval, but was approved by the University of Oxford Research Services (Project 12787).

2.3 Prospective surgical cohort interfacing with routine care: UK Hand Registry (Chapter 5)

The UK Hand Registry (UKHR) was included in this thesis to better understand the role of surgery in the treatment of BTOA from a clinical perspective, and to appraise the role of independent, prospectively collected registries as an observational data source in surgical epidemiology.[21] The study undertaken in chapter 5 has added to the clinical literature, but also highlights some significant weaknesses in this form of data source from a methodological perspective.

2.3.1 Introduction

The British Society for Surgery of the Hand (BSSH) developed the UKHR, formerly known as the BSSH audit database) in 2011 to develop a dataset of routine surgical practice akin to prospective national registries in other areas of surgery.[136] Whilst in its infancy, the UKHR enables collection of PROMS and operative information. This provided a unique opportunity to explore the role of surgery in treating hand conditions on a national level, identifying trends in practice of BSSH members. The data set contains patient reported outcome measures (PROMS) collected at baseline, three, six and 12 months following surgery, using EQ5D index as a general quality of life measure and the Patient Evaluation Measure (PEM).[137-139]

2.3.2 Data collection

All BSSH members are invited to participate in the UKHR. It currently includes adult patients only and only those undergoing elective surgery for a selective set of hand conditions, with operating surgeons prospectively inviting their patients for inclusion in the registry. There is no obligation to include all patients, with all participation from both surgeon and patient being voluntary. Full consent from each patient was gained for inclusion in the registry, and it can include patients undergoing surgery in both NHS and private practice. The operating surgeon completes the details of surgery within the online platform (https://www.ukhr.net), but collection of PROMs was undertaken remotely using text messaging, email or postal mail via the BSSH secretariat not working with the operating surgeon. The study in chapter 5 is based upon a secondary use of data for patients who underwent surgery for BTOA, using data anonymised prior to release to the research team.

2.3.3 Data Quality

This dataset contains only age, sex and surgical procedure undertaken in addition to the PROMS. There currently no available tool within the UKHR to assess data quality, or to determine the level of inclusion bias. The operating surgeon completes the initial information, proposing that the surgical information is likely to be clinically correct.

2.3.4 Missing data

For delta changes in PROMS, pairwise deletion was undertaken with an available case analysis approach. For the mixed effects model, the model estimated the values of missing datapoints, based upon it being missing at random. Data was not imputed.

2.3.5 Data Processing

An anonymised extract was released from the UKHR for the study. STATA 15.0 was used for the main analysis of the change in PROMS following surgery, with R3.5.0 for mixed regression models.

2.3.6 Advantages and Disadvantages

There are very few hand surgery registries worldwide. HAKIR, the Swedish Hand Registry is compulsory, and collects data on both elective and trauma surgery.[140] However, due to international trends in the surgery undertaken for BTOA, HAKIR contains predominantly patients who undergo trapeziectomy with ligament reconstruction. Ligament reconstruction

also predominates in the US, and therefore UKHR offers the unique opportunity to compare simple trapeziectomy alone to trapeziectomy with ligament reconstruction.[92, 109, 111] Collection of serial patient reported outcome measures is known to be difficult within routine clinical practice, and the rates of baseline PROM collection in the UKHR are favourable to other musculoskeletal registries.[136]

There is a significant risk of selection bias in this registry. It is not compulsory, and it is likely to reflect the patients undergoing surgery with surgeons who are BSSH members, active in evidence-based medical practice. This makes results generating less generalisable to everyday practice. Similarly, there is no requirement to add consecutive patients, and without further information it is difficult to see why one patient has been recruited and not another. When comparing the number of patients in the UKHR that covers all the UK to the surgical activity identified for England in HES, it emphasises the small number of cases captured in the dataset. No information is given as to why patients may be selectively included or excluded, or why patients may decline to participate. Whilst the PROM completion is better than seen in other areas, there is still a large attrition of patients completing follow up PROMs. The only method of addressing potential bias generated by those who do not complete questionnaires is to compare baseline demographics. As this unfortunately includes only age and sex, it is difficult to determine whether dissatisfied patients who have had a poor post-operative outcome have declined to participate.

2.3.7 Approval

The University of Oxford Clinical Trials and Research Governance team confirmed exemption from ethical approval for all UKHR research used anonymised data. Approval from the BSSH Audit committee chair was also gained for the secondary use of the data in this study.

2.4 Prospective Cohort Study: Million Women Study (Chapter 7)

2.4.1 Introduction

Million Women Study (MWS) provided this work with a different perspective: using an established prospective cohort study linked to routinely collected data. This provided the opportunity to 'recycle' the rich phenotypic information curated within the study to augment the surgical information within HES APC, and to analyse the potential risk factors for disease development from endogenous female hormones that would otherwise not have been possible.

2.4.2 Setting

The cohort profile of the MWS has been published elsewhere.[141] Between 1996-2001 the Million Women Study recruited 1.3 million participants aged 50-64 years from women who attended routine NHS breast screening at one of 66 centres in England or Scotland. All participants gave written consent, and completed questionnaires detailing their sociodemographic characteristics, medical history and lifestyle (www.millionwomenstudy.org). Participants have resurveyed every three-five years after recruitment. The MWS cohort includes one in four women born in the UK between 1935 to

1950, with virtually complete follow-up through ongoing linkage to UK National Health Service (NHS) Central Registers including cancer registrations, deaths and hospital admissions. MWS is also linked to CPRD, but this was not used in this work due to the surgical focus of this study.

2.4.3 Data collection

Questionnaires focussed upon factors not easily or routinely collected in many forms routinely collected data such as lifestyle (sleep, diet, exercise, alcohol and smoking habits) in addition to education, Body Mass Index (BMI), and socioeconomic deprivation. Of particular interest were historical reproductive factors and endogenous female hormonal factors such menarche, menopause, parity, breastfeeding history that are very poorly recorded elsewhere. This data is linked to HES APC in England from 1 April 1997 and Information Services Division (ISD) in Scotland from 1 January 1981 and therefore provides information on all NHS secondary care episodes including day case admissions and ONS mortality.[128, 142] Incident CTS and BTOA were identified through linkage using the code lists in Appendix A tables A.1 and A.2.

2.4.4 Data Quality

CTS and BTOA outcome definitions were based upon the validation work undertaken in UK Biobank and in MWS itself as described within the HES APC section 2.2.3, Chapters 3.3.2 and 4.3.2 and Appendix A.

2.4.5 Missing data

Missing data (<5% for any variable) were considered missing at random and were therefore kept in the final dataset to contribute to analysis where data was complete. For each variable, women with missing data were assigned to a separate category, ensuring that all comparisons were made within the same group of women. Overall loss to NHS follow-up in the Million Women Study is <1.5%, mainly through emigration.[141]

2.4.6 Data Processing

A data extract from the main database was generated by two statisticians in the Million Women study (Kirstin Pirie, Sau Wan Kan). This extract contained all information from all questionnaires in addition a binary variable if the participant was identified as having undergone an intervention for CTS or BTOA in HES APC, and the date of this intervention. Prevalent and incident CTS or BTOA disease was defined around the date of recruitment to MWS, and both analyses undertaken separately. Statistical analysis was undertaken in STATA version 15 within the Nuffield Department of Population Health (NDPH) server.

2.4.7 Advantages and Disadvantages

MWS has the huge advantage of capturing a significant proportion of women born in the UK between 1935-1950. This gives the cohort statistical power. The data is prospectively collected with very complete data and follow up of over 20 years. Emigration and opt out of the study are low, enabling excellent follow up through linkage to routinely collected secondary care and ONS mortality data.

The richness of data captured within MWS offers the opportunity to adjust for confounders of socioeconomic status, nutrition, sleep, alcohol and smoking with in-depth data. The study of endogenous female factors is also a unique opportunity, as investigating factors such as menarche, menopause, parity, age at first birth, breastfeeding history would not be possible within many other datasets or would be at risk of confounding due to a lack of adjustment for lifestyle factors such as BMI or socioeconomic status. Whilst not used in the study in chapter 7, MWS has repeated measures through the repeat questionnaires over time to determine changes in exposure, enabling analysis of time varying confounding.

The disadvantages of this dataset surrounding the selection bias of participation. It includes women who were presenting for breast cancer screening, and who were willing to participate. These women are likely to be more engaged with healthy lifestyle choices and healthcare services, disproportionately representing the general population. Similarly, the women participating would require a sufficient level of literacy in English to interact with the study and remain active at follow up with a stable postal address for surveys. 96% of participants consider themselves of white ethnicity, and therefore the cohort is less representative of a modern multicultural society. There has been no new recruitment since 2001 and therefore this cohort continues to get older without the ability to investigate younger women and the potential temporal change in reproductive factors. This is potentially pertinent considering the interaction of hormonal replacement therapy (HRT) with the incidence of surgical hand disease and the temporal changes in HRT use over the past two decades. Whilst very few women emigrate or request removal from the study, there is significant attrition of completion of later questionnaires. The study in chapter 7 was designed to only use data collected at baseline and therefore this loss of information

does not directly impact this work, but still be noted as a potential disadvantage of the dataset.

Incident hand disease could only be identified using HES APC, and therefore the potential weaknesses of using an administrative secondary care dataset remain present. This is less important as the outcome is validated and defined, without the need to link to surgical complications or separate by laterality. Incident cases would reflect only surgically managed disease and therefore the investigation of aetiology in this study reflects the association of endogenous female hormonal factors with undergoing surgical management. This may reflect an association with a more severe disease phenotype, but this is also confounded by the influence of health seeking behaviour and healthcare factors such as referral to secondary care and the decision to proceed to surgery. Compared to other more recent prospective cohort studies, there is minimal additional data collected about participants outside of the questionnaire (for example serum, DNA, other measurement data). This reduces the possibility of extensions to the study in chapter 7, for example by using serum hormone levels or in combined epidemiological and genetic studies such as mendelian randomisation studies.

2.4.8 Approval

Ethical approval was granted from the Anglia and Oxford Multi-Centre Research Ethics Committee. MWS cohort profile is described in more detail and data access policies for the MWS are available via the study website (http://www.millionwomenstudy.org/).

2.5 Federated Network analysis of International Routinely Collected Data: OHDSI (Chapter 8)

2.5.1 Introduction

When designing this thesis in 2017, the aim of this chapter 8 was to interrogate UK based primary care dataset (CPRD) as the gold standard epidemiological dataset for pharmacoepidemiology. CPRD has the advantage of longitudinal follow up in a sample of 8% of the UK population representative of the general population, and the ability to identify less severe health conditions and outcomes associated with prescribed medications.[143] As the study developed, the Observational Health Data Sciences and Informatics (OHDSI) network emerged and therefore the brave decision to run this study as a federated network analysis was made.

2.5.2 Setting

OHDSI is an international community of data partners who share a common goal of improving global observational research. It contains members from academia, industry, government and regulatory bodies, aiming to produce open source, collaborative research through large scale analytics.[24] The European Health Data and Evidence Network (EHDEN) is part of the EU based innovative medicines initiative (IMI) and sits as the driver of European engagement and participation within the OHDSI network.[23] The work in chapter 8 was developed with partners in EHDEN with aim of encouraging future European collaborative work in the OHDSI community.

OHDSI enables federated network analyses on patient level data to be undertaken using a variety of data sources, all mapped to the common data model (CDM). Columbia University, NY, USA is the central coordinating centre.[144] A study is developed by one member of the community and offered freely to other members to participate. All participation is voluntary and based upon collaborative work in an iterative, open science approach.

2.5.3 OMOP CDM

The Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) is the foundation upon which the network is based.[27] Similar to an electronic travel adaptor, it enables data in very heterogenous data sources to be compared through harmonisation. It gives the data a common terminology and format, enabling them to be used within standardised data tools and software packages for analysis and curation. The CDM accommodates standardised clinical person/patient data, health system data, health economic data and metadata using a standardised vocabulary (Figure 2.1).

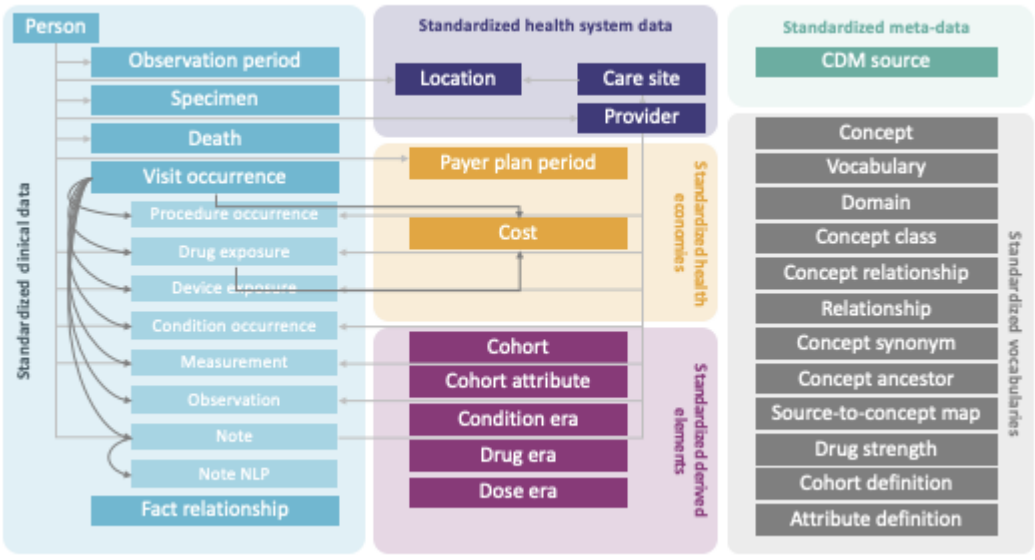

Figure 2.1 The OMOP CDM structure

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A data source is first mapped to the common data model through an extraction, transform and load (ETL) process. This can either be undertaken by data scientists within an institution, or by a third party. In EHDEN, this is recommended to be undertaken by an accredited technical small or medium enterprise (SME) who can assess data quality following transformation. Once mapped to OMOP CDM, any standardised analytics can be undertaken at source without the need for data sharing outside an institution. Privacy by design is baked into the network's principles, with all data remaining within the collaborating site and interaction at an aggregated level only (Figure 2.2). Standardised analytical packages can be generated using OHDSI written open-source software from the OHDSI Methods library using R and can also be written using the ATLAS™ interactive analysis platform.[145]

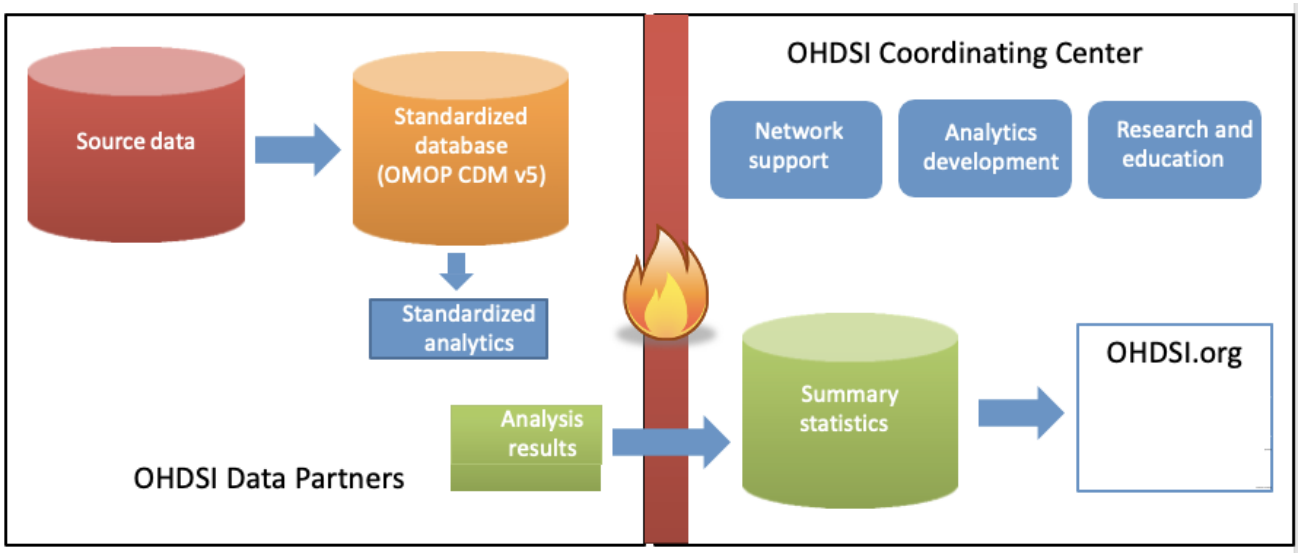


Figure 2.2 OHDSI data journey

ATLAS™ is a freely available web-based platform for community members who are less proficient in computer programming. It is based upon a selection of packages within OHDSI method library. Its main use is to generate cohorts (known in OHDSI as phenotypes) even for those who go on to develop the standardised package within R outside of ATLAS™ .

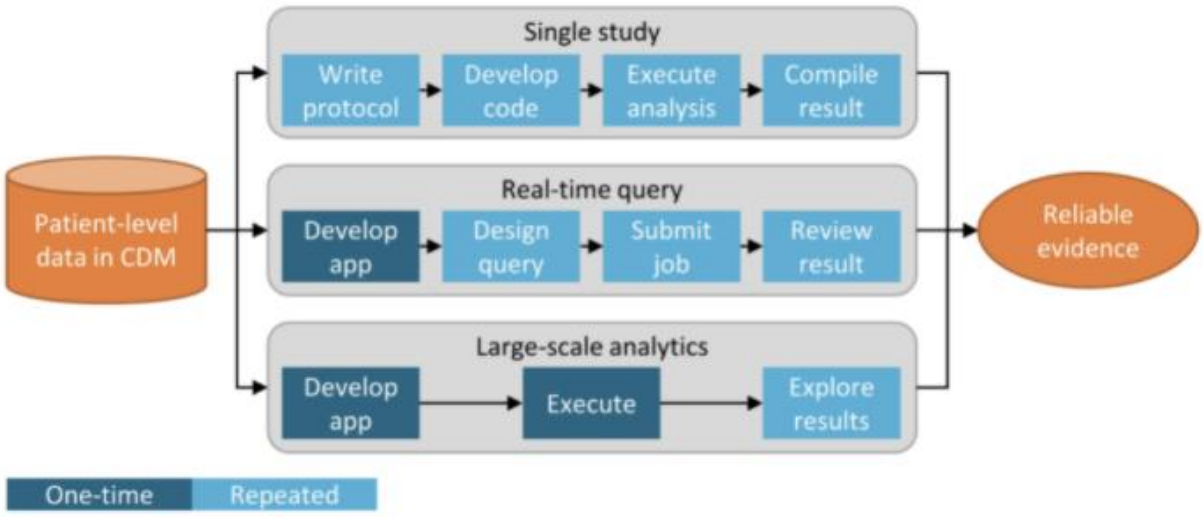


Figure 2.3 Different potential pathways in study development and design in OHDSI (Reproduced from The Book of OHDSI, under Creative Commons Zero v1.0 Universal license)

A public instance of ATLAS™ can be used freely for those without data as a way of designing an analytical package by data partners in the community, but for those in the community who are data owners, ATLAS™ can also be linked to their OMOP CDM mapped data. This enables studies to be run in real time and generate results rapidly throughout the study design journey. ATLAS™ linked to a data source can be used to run feasibility counts in the infancy of study design, to develop cohort definitions, and to identify incidence rates, but can then be used to also generate more complex processes described as '*cohort pathways'*, '*population level estimation'* studies and '*patient level prediction'* studies. Cohort pathways can be used to show the clinical journey of data source participants through healthcare in combination with more granular characterisation of a generated patient cohort. Patient

level prediction (PLP) enables generation of analytical package to determine if outcome can be predicted from a combination of exposures in a prediction model. As the name suggests, this is based at an individual patient level. Population level estimation (PLE) packages generate studies of causal inference and risk factor association studies including comparative cohort studies. In Chapter 8, a PLE causal inference study was designed and undertaken through study development in OMOP CDM mapped CPRD. This was then shared within the community and replicated in other data sources.

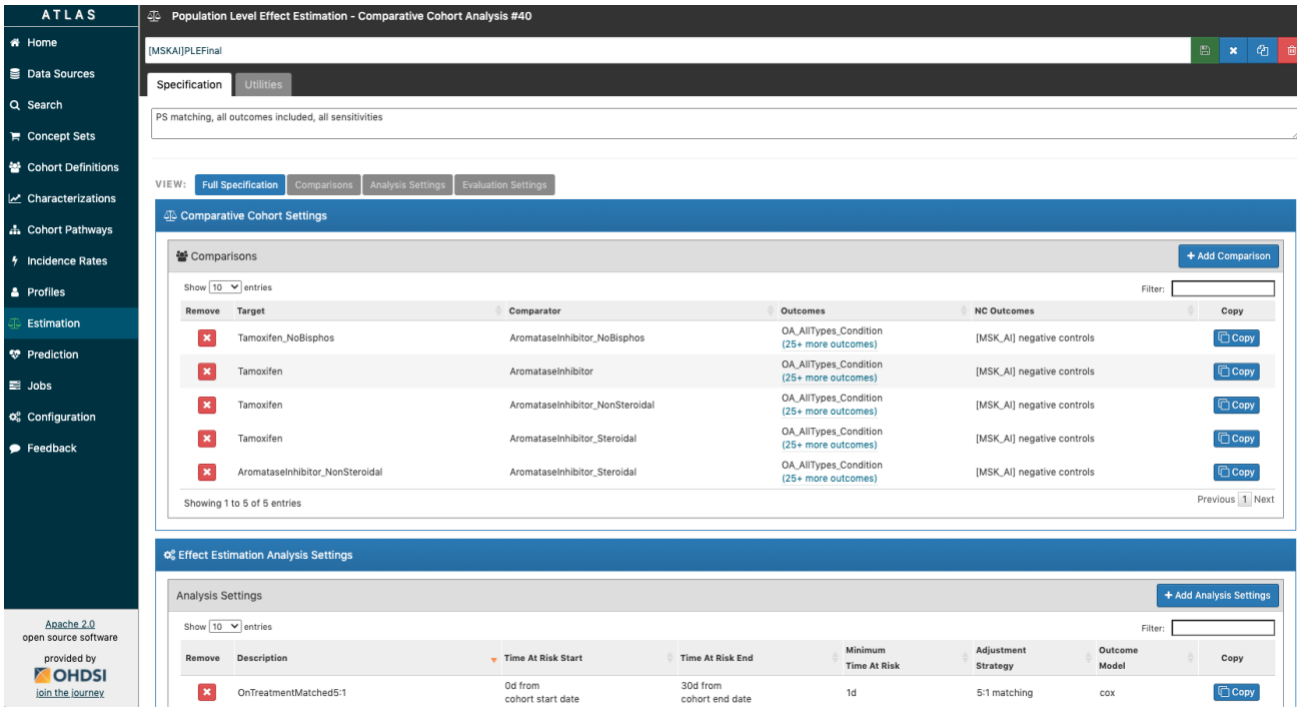


Figure 2.4 ATLAS™ software platform for study generation, Population Level Estimation (PLE) settings
(image reproduced under Apache 2.0 License)

2.5.4 Data sources

Data processes are dependent upon which dataset in the OHDSI community is being investigated. In this study the data sources used are a combination of Electronic Healthcare Records (EHRs), administrative claims data from private and national insurance providers,

and nationally collected primary care data. Combined into a federated network analysis through assimilation of all datasets into the OMOP CDM.

2.5.4.1 Included datasets in this study

19 datasets from 9 countries in the OHDSI and EHDEN community collaborated to run the study designed in CPRD (Table 2.1) All partners ran the cohort phenotypes in the cohort diagnostics, and 8 datasets ran the final PLE study package developed in Chapter 8.

Table 2.1 OHDSI collaborators datasets included in either cohort diagnostics or final PLE

Source	Population	Patients	Type	Also Included in PLE?
AUSOM	Ajou University Tertiary Hospital	2M	EHR	X
CIUMC	Columbia University Irving Medical Center/NY-Presbyterian Hospital	6.6M	EHR	X
CPRD	UK (primary care general population)	13M	EHR	X
IBM CCAE	US (commercially insured <65y)	142M	Claims	
IBM MDCD	US (Medicaid enrolees)	26M	Claims	
IBM MDCR	US (commercially insured >=65y)	10M	Claims	
IQVIA LPD Australia	Australia (primary care general population)	3.1M	EHR	
IQVIA DA France	France (primary care general population)	7.8M	EHR	
IQVIA DA Germany	Germany (general population)	34M	EHR	
IQVIA Hospital Chargemaster	US (Administrative billing data)	>86M	Claims	X

IQVIA LPD Belgium	Belgium (primary care/ outpatient general population)	2M	EHR	X
IQVIA Openclaims	US (commercial claims)	>200M	EHR	X
JMDC	Japan (insured general population 18-65y)	5.5M	EHR	
Optum PanTher EHR	US (general population)	>95M	EHR	
Optum Clinformatics SES	US (commercially insured)	85M	Claims	
Pharmetrics	US (medical and pharmacy claims)		Claims	
SIDIAP	Catalonia (primary care general population)	7.7M	EHR	X
SIDIAP_H	Catalonia (primary care general population linked to hospital care)	2M	EHR	X
STARROMOP	Stanford (hospital)	>2.7M	EHR	

2.5.4.2 Ajou University- South Korea

Ajou University hospital is an inpatient and outpatient EHR for the tertiary care centre in Suwon province, Korea. It includes condition, procedure, prescription, observation and mortality data.

Start date: 1994

2.5.4.3 Columbia University Irving Medical Centre (CUIMC)- NY, USA

This US quaternary health centre EHR includes inpatient and outpatient care from CUIMC, and primary care from northern Manhattan.

Start date: 1989

2.5.4.4 Clinical Practice Research Datalink (CPRD) GOLD- UK

This dataset generated by Vision software in UK general practice is considered 'gold standard for pharmacoepidemiological studies.[143] It is considered to the representative of the general population and includes 8% of the population. It is a national primary care dataset that includes mortality data as well as conditions, prescriptions and vaccinations, measurements, observations and referrals to other care settings.

Start date: 1989

2.5.4.5 IBM MarketScan® Commercial Claims and Encounters (CCAE)- USA

This is a US based administrative claims data source that includes data from individuals in insurance health plans that are sponsored by their employers. It includes data from employers and health plans in addition to the adjudicated health insurance claims. It includes a variety of different healthcare plans and covers both inpatient and outpatient services including prescriptions and laboratory investigations.

Start date: 2000

2.5.4.6 IBM MarketScan® Multi-State Medicaid (MDCD)- USA

Medicaid is a health insurance dataset from the US that gives health cover to low income people including children. It includes adjudicated claims for inpatient and outpatient services and prescriptions. Unlike CCAE and Medicare, it does not contain laboratory

investigations. Episodes in the dataset can be linked over gaps in cover as patients keep their same identifier throughout.

Start date: 2006

2.5.4.7 IBM MarketScan® Medicare (MDCR)- USA

Medicare is a health insurance dataset from the US that covers retirees with either their primary health cover, or as an additional cover to their private insurance. It includes adjudicated claims for inpatient, outpatient, prescription and laboratory services.

Start date: 2000

2.5.4.8 IQVIA Australia Longitudinal Patient Data (LPD)

This primary care dataset covers approximately 150 GP practices in Australia, including all patients within each practice. It includes conditions and prescriptions, observations and measurements like CPRD, but does not include any referral information or secondary care data.

Start date: 2006

2.5.4.9 IQVIA Disease Analyzer (DA) France

This dataset is generated from primary care records and medical centres from France and includes all patients within each practice. It includes conditions and prescriptions but does not include secondary care data.

Start date: 1997

2.5.4.10 IQVIA Disease Analyzer (DA) Germany

This dataset is generated from primary care records and medical centres from Germany and includes all patients within each practice. It includes conditions and prescriptions, laboratory data and some connections to specialist practices, and referral to secondary care.

Start date 1992

2.5.4.11 IQVIA Hospital Charge Data Master- USA

This dataset represents combined data for remuneration, that uses claims from hospital charge data masters and resource management systems. It includes claims for inpatient secondary care in non-federal hospitals, and includes in prescriptions, conditions and procedures with up to 530 million medical events included

Start date: 2007

2.5.4.12 IQVIA OpenClaims- USA

This dataset is of pre adjudicated reimbursement claims with a subset that are adjudicated. It includes outpatient, office based care in addition to secondary care remuneration systems.

Start date: 2013

2.5.4.13 IQVIA Longitudinal Patient Data (LPD) Belgium

This dataset contains both EHR and longitudinal data from outpatient and ambulatory care. It covers 688 sites and 140 million records, and includes conditions and prescriptions, laboratory and pathology reports and measurements.

Start date: 2005

2.5.4.14 Japan Medical Data Center (JMDC)

This dataset includes 60 different health insurance plans for workers 18-65 years and their families. It includes claim data for inpatient and outpatient services, conditions, procedures and prescriptions.

Start date: 2005

2.5.4.15 Optum Pan-Therapeutic Electronic Health Records- (Optum Panther)- USA

This dataset contains secondary care in addition to outpatient services, and includes conditions, prescriptions, laboratory results and procedures. It is known for having longer durations of care for included patients cover over 140,000 providers, with 45% included having activity of more than 3 years.

Start date: 2006

2.5.4.16 Optum Clinformatics Extended Data Mart- Socio-Economic Status (Optum SES)- USA

This dataset includes adjudicated claims for those with health insurance including Medicare in those over 65 years. Age is capped at 90 years for inclusion. It includes inpatient and outpatient care, prescriptions, laboratory test and also includes socioeconomic status of participants.

Start date: 2000

2.5.4.17 Pharmetrics - USA

This data includes both inpatient and outpatient services that can be linked between primary care, specialist care, medications and acute care. This gives the advantage of a more longitudinal perspective for included participants.

Start date: 2015

2.5.4.18 Sistema d'Informacio pel Desenvolupament de la Investigacio a l'Atencio Primaria (SIDIAP) Catalonia, Spain

This dataset includes primary care for approximately 80% of the population of Catalonia, North-East Spain in a taxation based healthcare system. It includes prescription, condition, immunisation and referral to secondary care.

Start date: 2006

2.5.4.19 Sistema d'Informacio pel Desenvolupament de la Investigacio a l'Atencio Primaria- Hospitalisation linked data (SIDIAP_H) Catalonia, Spain

This is a subset of 2.5.4.18 that is linked to secondary care inpatient services in the Catalan Institute of Health hospitals and was used in study development in order to determine if greater information about surgical outcomes could be gained from this linked dataset.

2.5.4.20 STanford medicine Research data Repository (STARR OMOP) –Stanford University, California- USA

STARR OMOP represents Stanford Health care, Stanford Children's Hospital, Packard Children's Health Alliance clinics, and the University Healthcare Alliance. It is an EHR that also links to other elements of care such as radiology information from picture and archiving communication system (PACS).[146]

Start date: 2008

2.5.5 Data Quality

Within the network, data quality checks occur within every step of the extraction-transform-load (ETL) process of converting the dataset to the OMOP CDM to ensure that the raw data is fully represented in the mapped data. This is a process that occurs internally at each participating site, and within EHDEN supported member sites, SMEs are invited to become certified in enabling the ETL process as a further step in assuring data quality. Whilst data quality itself is very difficult to identify directly, processes have been designed within the

OHDSI network in order to generate a better understanding of data quality with data integration within the OMOP CDM, and then within data analysis.

In order to do this within study development itself, data quality was evaluated in two ways. Firstly prior to study design, the use of the data quality dashboard for the overall value of data sources included.[147] Secondly, the study specific data quality based upon the generated exposures, outcomes and study design that can be evaluated using the Cohort Diagnostics process.[148]

2.5.6 Validation studies- Cohort Diagnostics

Cohort Diagnostics is an OHDSI designed package and iterative process promoted by the community to develop better cohort definitions for use in studies. Designing patient cohorts that can be representative of a disease state throughout the network, between different countries and in varying types of data sets can be challenging and poorly developed cohort phenotypes threaten the reliability of the evidence generated. Patient cohorts are therefore designed by generating a concept set- a set of codes that are considered to define a particular disease state, outcome, procedure, or healthcare event. This is based upon standardised codes, and can be searched for within ATLAS™, examining the hierarchy of mapped source codes and CDM codes using the ATHENA tool.[149] Concept sets are then encased within a cohort definition, with inclusion criteria based upon demographic, disease and temporal factors to determine when a patient with enter and leave a cohort. Cohort definition or phenotype is a term within OHDSI that does not just cover the patient population included, but also the way in which exposure, interventions and outcomes are

defined. All generated cohort definitions can then be interrogated in each data partner offering to be a collaborator in a study if they run the unique cohort diagnostics package designed by the lead centre.

In this study, concept sets were designed within an iterative process with data partners in Europe and the US to identify the potential areas of difficulty in assimilating the data sources in one study. Cohort diagnostics enabled us for example to identify orphan concepts (data driven suggestions in the package for concepts that were not included but that either have a similar name or high record counts in the data), trend in incidence and trends over time to determine if the cohort definitions made reflected the clinical population that we were expecting. It also enabled us to identify the nuance of individual source codes mapped to CDM to improve our concept sets embedded within the cohort definitions to best suit our data partners.

The iterations of cohort diagnostics for the study in chapter 8 have been designed to be freely available and interactively appraised in a web placed platform shinyapps.io with the nuances identified in this study described within the methods section in chapter 8.3.1 [150-152]

Overall cohort diagnostics generates a browser that appears like Figure 2.5. The banner on the left shows the tabs available. Firstly, cohort counts enable identification of the raw number of patients identified within a cohort definition in each dataset. To follow this walk through of examples live, use

https://jenniferlane.shinyapps.io/CohortDiagnosticsMSKAI_FirstIteration

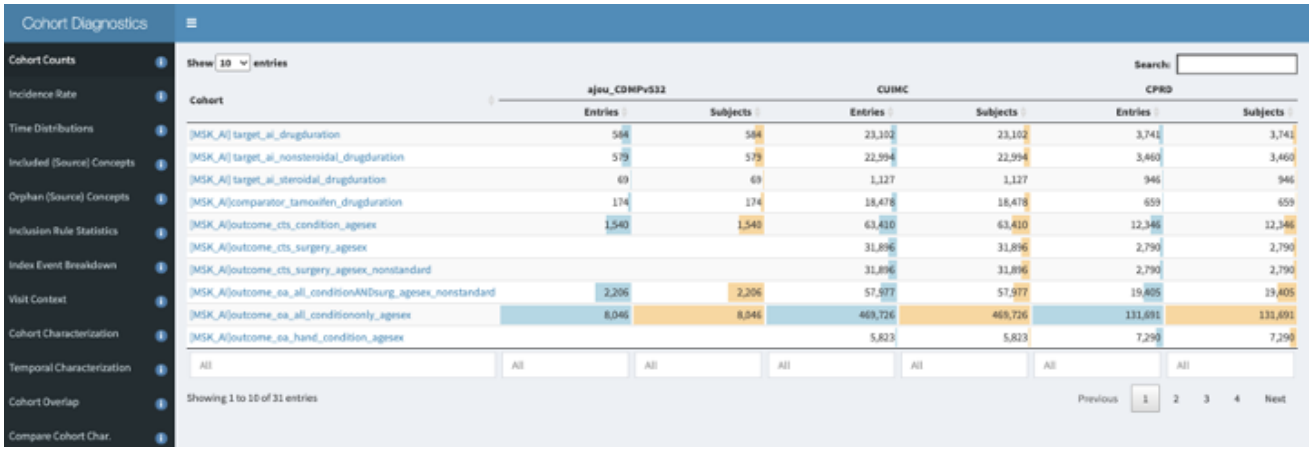


Figure 2.5 home screen indicating counts for each cohort definition in 3 datasets, generated cohort diagnostics page for study in Chapter 8

2.5.6.1 Evaluation of included concepts

The included source concepts tab enables comparison of datasets to evaluate the proportion of patients who have been captured into a definition by each code (Figure 2.6). This can be searched in the data sources source coding system, or within the CDM standardised system. This screen shot shows the difference in included source codes for the outcome definition of carpal tunnel syndrome between UK based CPRD (with READ codes), US Medicare (based upon ICD-9 and ICD-10 codes) and Catalan SIDIAP (also based in ICD-9 and ICD-10).

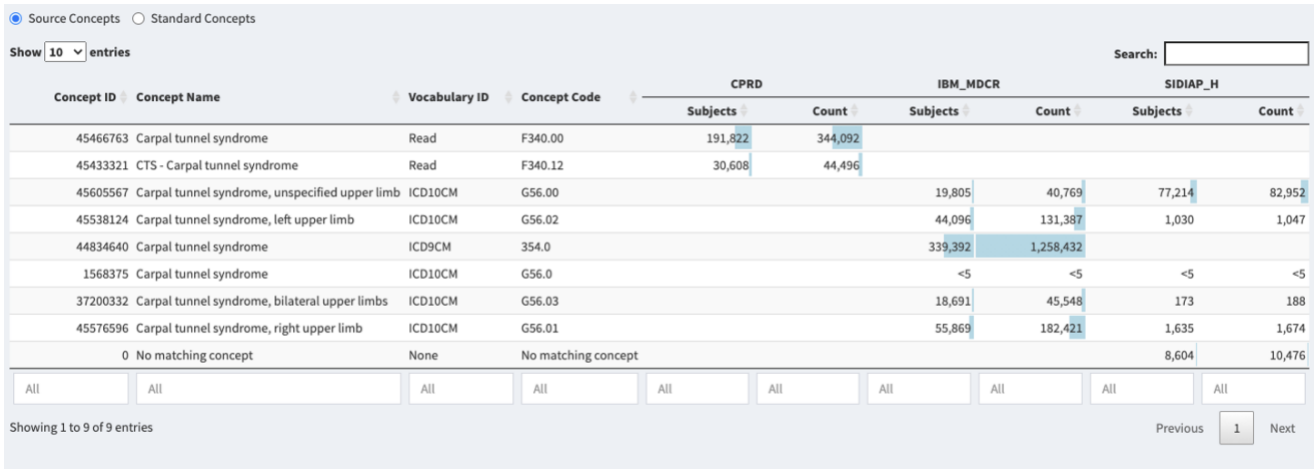
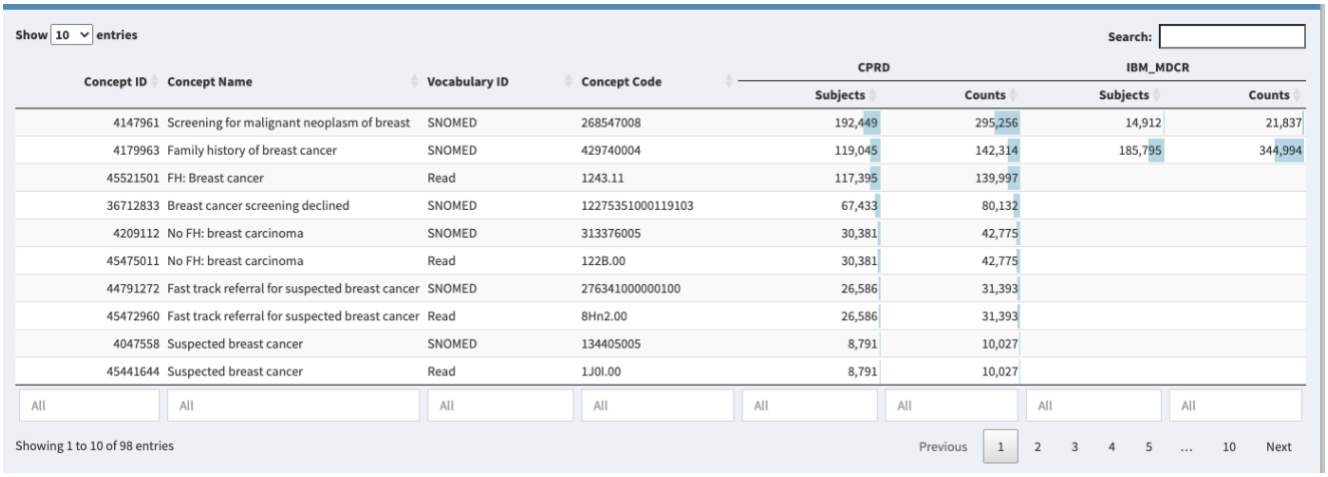


Figure 2.6 included source concepts in an example medical CTS definition, CPRD, US Medicare and Hospital linked SIDIAP

In an opposite data driven approach, the cohort diagnostics package will also suggest orphan concepts- concepts not included within your concept set that appear to be related to included terms (Figure 2.7). Here, an example of the concepts suggested for inclusion in the definition of breast cancer shows how breast screening is highlighted as a potential lost code.



Show 10 entries Search:

Concept ID	Concept Name	Vocabulary ID	Concept Code	CPRD		IBM_MDCR	
				Subjects	Counts	Subjects	Counts
4147961	Screening for malignant neoplasm of breast	SNOMED	268547008	192,449	295,256	14,912	21,837
4179963	Family history of breast cancer	SNOMED	429740004	119,045	142,314	185,795	344,994
45521501	FH: Breast cancer	Read	1243.11	117,395	139,997		
36712833	Breast cancer screening declined	SNOMED	12275351000119103	67,433	80,132		
4209112	No FH: breast carcinoma	SNOMED	313376005	30,381	42,775		
45475011	No FH: breast carcinoma	Read	122B.00	30,381	42,775		
44791272	Fast track referral for suspected breast cancer	SNOMED	276341000000100	26,586	31,393		
45472960	Fast track referral for suspected breast cancer	Read	8Hn2.00	26,586	31,393		
4047558	Suspected breast cancer	SNOMED	134405005	8,791	10,027		
45441644	Suspected breast cancer	Read	1J0I.00	8,791	10,027		

All All All All All All All All

Showing 1 to 10 of 98 entries Previous 1 2 3 4 5 … 10 Next

Figure 2.7 Orphan concepts suggested for concept set defining history of breast cancer including record counts in CPRD and US Medicare

2.5.6.2 Evaluation of cohort definition

The incidence rate tab enables comparison of rates represented by cohort definitions between data sources, over time, and restricted by age and sex. This is useful in determining if the cohort definition represents the clinical population expected through the inclusion criteria throughout the data sources and in designing the included timeframe for the final PLE study. The screen shot in Figure 2.8 shows that the definition for new users of aromatase inhibitors that is restricted to patients starting drug use after 2006, with recorded female sex, and over the age of 55 appears consistent.

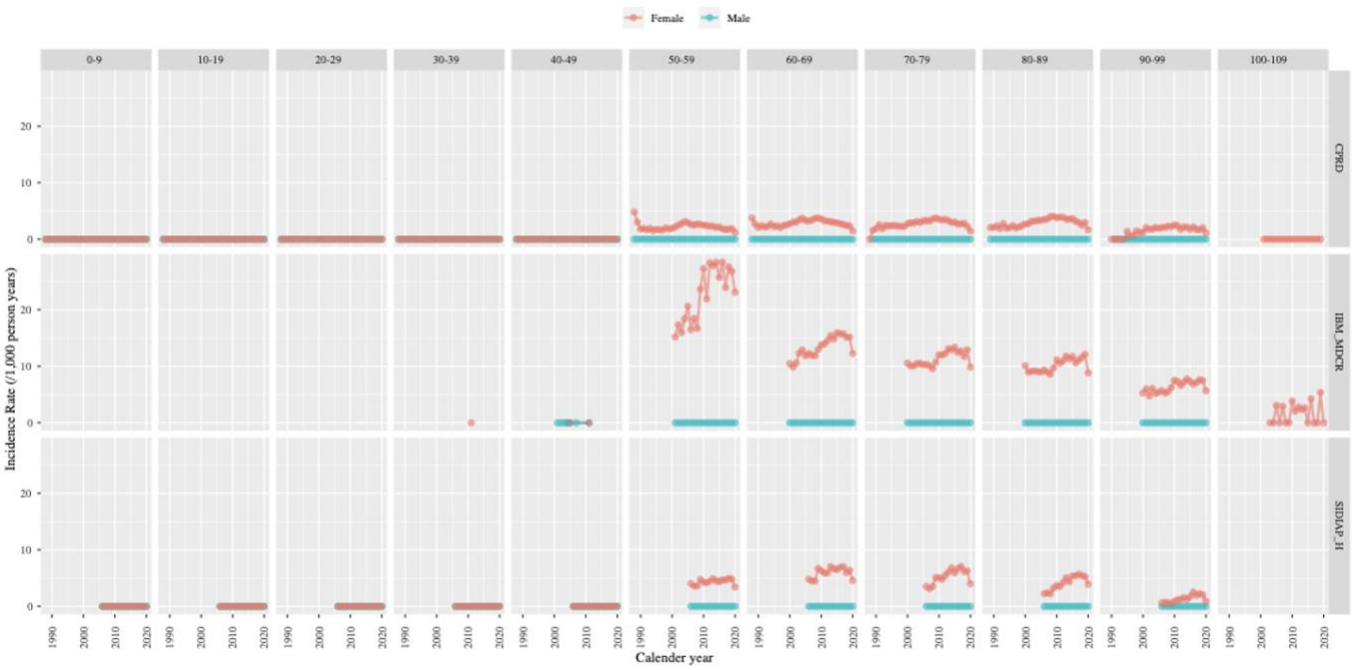


Figure 2.8 Age and sex adjusted incidence of new users of Aromatase Inhibitors over time, CPRD, US Medicare and Hospital-linked SIDIAP

Attrition of patients can be also identified within inclusion rule statistics, to identify if a cohort definition is appropriately excluding patients who do not have the required characteristics within the data (Figure 2.9).

Target cohort:

Target: [MSK_AI] target_ai_drugduration (n = 584)

Show 10 entries Search:

Rule Sequence ID	Rule Name	CPRD				IBM_MDCR				SIDIAP			
		Meet	Gain	Remain	Total	Meet	Gain	Remain	Total	Meet	Gain	Remain	Total
0	breast cancer	5,437	30,651	30,651	51,091	2,658	55,318	55,318	61,058	9,464	19,719	19,719	37,780
1	Age=>55	2,297	42,690	27,197	51,091	27	60,996	55,284	61,058	2,627	29,470	16,832	37,780
2	excluding prior tamoxifen use	4,009	31,759	23,162	51,091	7,764	52,400	47,410	61,058	255	30,638	16,575	37,780
3	Female sex	60	50,796	23,102	51,091	201	58,406	47,209	61,058	35	37,566	16,540	37,780

Showing 1 to 4 of 4 entries Previous 1 Next

Figure 2.9 Inclusion criteria for the cohort definition of new users of aromatase inhibitors, with number of records excluded by each criterion in CPRD, US Medicare and SIDIAP

Further analysis of the demographics of included populations within a cohort definition is given in cohort characterisation (Figure 2.10). The ‘pretty’ tab provides a generic set of

demographic factors that are thought to be most influential in identifying potential confounders, but within the 'raw' tab one can appraise any variable that may be present in the mapped data within the searchable function.

Target cohort:

Show 100 entries Search:

Covariate Name	CPRD (n = 63,410)	IBM_MDCR (n = 243,792)	SIDIAP_H (n = 26,912)
	Proportion	Proportion	Proportion
Age group			
55 - 59	28.7%	1.1%	28.3%
60 - 64	17.6%	1.4%	18.8%
65 - 69	13.2%	30.1%	14.0%
70 - 74	11.8%	23.1%	12.8%
75 - 79	11.3%	18.9%	11.7%
80 - 84	9.6%	14.2%	8.9%
85 - 89	5.6%	8.1%	4.3%
90 - 94	1.8%	2.7%	0.9%
95 - 99	0.3%	0.5%	0.1%
100 - 104	0.0%	0.0%	
Gender: female			
Gender = female	100.0%	100.0%	100.0%
Medical history: General			
Acute respiratory disease	9.0%	20.5%	17.7%
Attention deficit hyperactivity disorder		0.2%	0.0%
Chronic liver disease	0.1%	1.1%	1.8%
Chronic obstructive lung disease	1.5%	9.0%	3.3%

Figure 2.10 Patient characteristics of a cohort definition using the 'pretty' tab for suggested pertinent demographic factors in 3 datasets

Finally, the ability to compare the overlap of cohort definitions is also useful to ensure that discrete populations have been made (Figure 2.11). Here the definitions for new users of aromatase inhibitors and new users of tamoxifen are calculated, and the definition was designed to exclude those with a prior use of the other drug. This plot shows that no overlap exists in the three example datasets, therefore implying that the cohort definition has appropriately generated discrete populations.

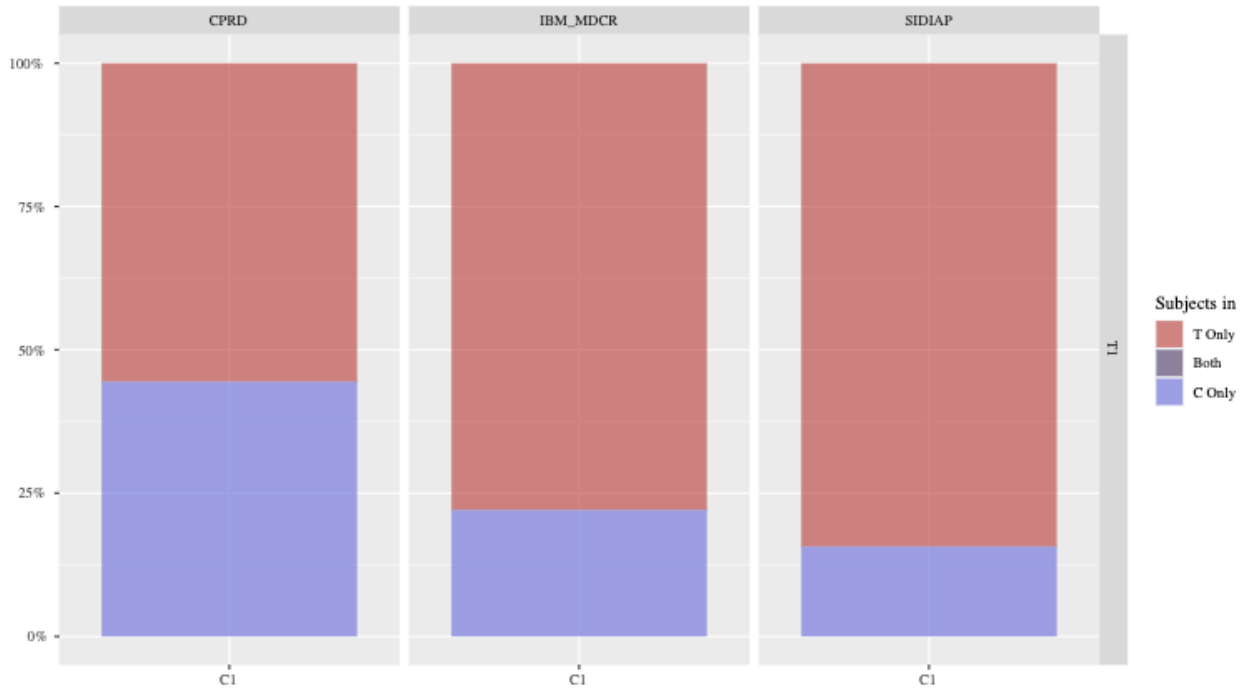


Figure 2.11 Cohort overlap between new users of aromatase inhibitors and new users of tamoxifen in CPRD, US Medicare and SIDIAP

Overall, Cohort Diagnostics is an iterative process of defining cohorts, running the cohort diagnostics package, identifying issues such as unusual trends, or recognition of orphan codes. Subsequent redefining of cohorts and rerunning of the package after discussions with collaborators in order to make the best possible study design. In the study detailed in chapter 8, three formal processes were undertaken with collaborators to iterate. Details of the findings in this process are given in the results section 8. [150-152]

2.5.6.3 Evaluation of data sources

The overall patient counts show the feasibility of running the final PLE analysis in each dataset and the ability of the data source to contribute. In addition to this, cohort diagnostics can suggest whether a dataset should be included in only certain analytical elements of a study through comparison of longitudinal element of the data. The time

distributions function is a useful method of comparing the longitudinal follow up of included patients, and the potential for a data source to contribute to different analyses. Here, the difference in the number of days a patient is present within CPRD, Medicare and SIDIAP is shown, emphasising the advantage of longitudinal data capture in CPRD, and the potential risk of poor past medical history capture within Medicare.

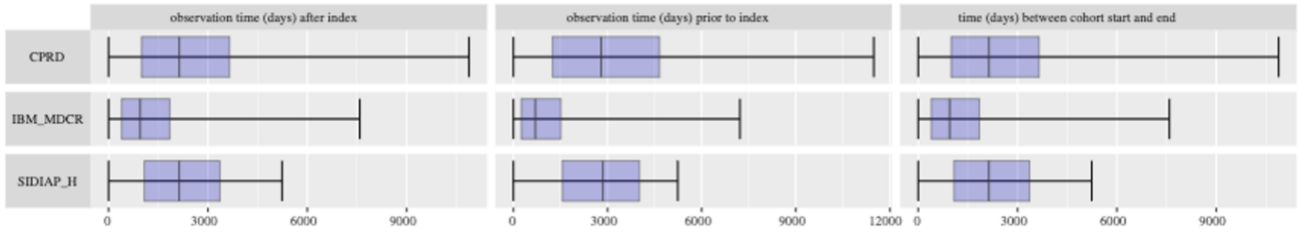


Figure 2.12 Time distributions shown in Cohort Diagnostics platform for an example cohort definition in CPRD, US Medicare and Hospital linked SIDIAP

Data quality analysis was subsequently undertaken once analysis was complete prior to unblinding of results. This was undertaken using the Evidence Explorer package described below to determine if dataset should contribute to the final analysis.

Data Processing

In this study, the ATLAS™ tool was used linked to the Oxford OMOP CDM mapped CPRD instance to give record counts for our dataset. The PLE was designed within ATLAS™, to generate the comparative cohort settings, effect estimation determinants, determine how the analysis would be set up including the large-scale data driven propensity score analysis and outcome model. The study was run in CPRD using an amazon web server-based R environment. The analysis was then run as a distributed network format, similar to other areas of pharmacoepidemiology such as Canadian Network for Observational Drug Effect Studies (CNODES).[26] Generated standard analytical packages were generated and shared,

but all data remains at source. This encompasses the 'privacy by design' element of the network analysis, where only aggregated results are shared, with no individual patient data leaving the home institution.

All collaborators shared their aggregated results generated from the shared PLE package in an established area SSH File Transfer Protocol server. These were then combined into one output within the Oxford AWS R environment, and then created into a R shiny output to graphically show and compare results.

Evidence explorer

The OHDSI EvidenceExplorer package was used to generate an interactive web-based shiny app using shinyapps.io.[153] All results were blinded whilst appraising diagnostics such as propensity score models, covariate balance and systematic error to determine the risk of observed and unobserved confounding. This was generated as a web-based platform to enable easy appraisal and comparison of aggregated results by the international collaborators, with small numbers minimised to prevent secondary disclosure of data.

Advantages and Disadvantages

Working within an open science community like OHDSI offers huge advantages. From a data perspective, there is a large variety of heterogenous data sources, from heterogenous healthcare systems in an international community. This offers the unique opportunity to externally validate analysis generated in CPRD, and to robustly explore if the associations found are a product of the included population, the healthcare system, or a nuance of

surgical practice within one country. The data remaining within the host institution with analysis occurring behind host firewalls with only aggregated results being shared generates a network with privacy by design and enables of collaborative working without compromising on data security. The OHDSI community continues to expand generating increasing possibilities for collaboration, with over 98 partners in the EHDEN network alone, with CDM mapping beginning in more countries in South America and Asia.

From an analytical perspective, the use of standardised code and web-based platforms such as ATLAS™ also reduces the time taken to run a real time query within the data itself. It offers the opportunity to gain expertise from colleagues outside of your institution and a clinical community that you may not have otherwise met. This interdisciplinary working becomes symbiotic, with the clinical expertise offered by academic clinicians enabling a greater insight into patient conditions and clinical practice that would have been missed by a team of data scientists alone. Generating analysis within the standardised analytic package and the CDM greatly also increases the ease of international collaboration, with others in the network able to check your code, especially as all code is encouraged to be freely available for appraisal.

The community encourages an open science approach to all elements of research, which has the benefit of promoting a robust research approach. Prior published protocols facilitate local ethical approval at collaborator sites and generating web-based data platforms for open appraisal of included cohorts provides a forum for everyone to see the results. The transparency, visibility and reproducibility of the research process improves the nature of results generated and promotes a reduction in research waste. Initiatives such as the

phenotype library enable researchers to share their cohorts with the community, enabling transfer of knowledge and an efficient research process.[154]

Despite these advantages, there are disadvantages in a federated network approach. As all data remains at source and is pseudonymised, one cannot identify if a patient is included in more than one dataset. This is not necessarily an issue in most European datasets but could cause patients to be duplicated in datasets where patients may drop in and out of insurer or claims datasets, or there is cross over between regional and national EHR/ administrative records. Similarly, as the data is not combined, a smaller research site may not be powered to run an association study alone but can provide patients for meta-analytical estimates.

The ETL process to the CDM may cause loss of granularity for some conditions. This is checked during data quality processes but is particularly pertinent when discussing surgical observational studies in the network. Surgical epidemiological studies in OHDSI and EHDEN are in their infancy, and procedures classification in the CDM is known to be an area where further development is needed. As a dynamic community this is something that will improve in future, but the study in Chapter 8, especially in cohort diagnostics identified this as an issue.

Finally, for those who are not advanced programmers, research is limited to the packages within the OHDSI methods library already generated. This became a limitation when designing the study in Chapter 8, as there is currently no community package designed to incorporate a competing risk analysis. The community is open to developing new packages, but this takes time, and was outside the scope of this thesis. The promising result is that the

work in chapter 8 has since been used as a proof-of-concept package to develop a competing risk analysis model, emphasising that there is a role for symbiotic, collaborative work within this community.

Approval

The study protocol was registered with EU (number EUPAS38362)

http://www.encepp.eu/encepp/viewResource.htm?id=38363

Each collaborator site gained individual IRB approval based upon EU PAS protocol; CPRD gained ISAC approval protocol 20_190R.

3. Administrative data (Part 1): HES APC

Trends in incidence of and risks of serious adverse events and revision surgery following Carpal Tunnel Decompression, Hospital Episode Statistics for England 1998-2017*

Contributions: All work and data in this chapter was curated, designed analysed and interpreted by myself apart from assistance within validation studies. In section 3.3.2. Mr Wee Leon Lam and Dr Lucy Popplewell assisted as second reviewers of patient notes with data extract for the validation study generated by Dr Christian Schnier in UK Biobank and senior advice from Prof Cathy Sudlow; Mr Akira Wiberg assisted as the second reviewer of patient notes with data extract for the validation study generated by Dr Angela Balkwill and Dr Kirstin Pirie for MWS. With thanks to Mr Richard Craig for his co-curation of the raw HES data, and senior advice from Prof Jonny Rees.

3.1 Summary

CTD surgery is widely used to treat CTS. This chapter explores the safety of the procedure in routine clinical practice in England and the patient factors that may be associated with increased incidence of SAEs and revision surgery. This study aimed to be the largest national study of CTD to date, providing the best available evidence on complications and revision

* Parts of this content has been published in Lancet Rheumatology, and as a conference abstract at BSSH Autumn meeting, October 2018 155. Lane JCE, Craig RS, Rees JL, Gardiner MD, Green J, Prieto-Alhambra D, et al. Serious postoperative complications and reoperation after carpal tunnel decompression surgery in England: a nationwide cohort analysis. Lancet Rheumatol. 2021;3(1):e49-e57.

rates within a nationalised healthcare system. This study provides benchmark estimates for the countrywide incidence and safety of CTD in England. A perimenopausal peak in CTD incidence was seen with an overall flat trend in surgeries undertaken over time. Overall risk of revision decompression was low at 3.4% (n= 29 288/855 838), with a median time to revision surgery within one year. Risk factors associated with the need for revision surgery included male sex, increasing age, comorbidity and socioeconomic deprivation. Risk of serious local complications was very low at 0.08% (n= 698/ 855 838) within 90 days of surgery.

3.2 Introduction

Many patients require surgery to decompress the carpal tunnel. In the USA, the estimated cost of surgically treated CTS in 1995 was $2 billion[31, 32]. Although surgery is successful in the majority of patients, some experience persistence of symptoms, especially if surgical decompression is delayed until constant nerve symptoms are present. Furthermore, a small proportion of patients suffer recurrence of CTS. CTS exacts a considerable socioeconomic burden on society, and its prevalence is increasing. [29]

There is a lack of well-defined estimates of the rate of complications and revision surgery following this common procedure. The majority of studies include cohorts from a single institution or region or have taken a sample of patients from insurance data.[115, 117, 156-159] There is difficulty in defining the incidence of revision surgery due to limitations in international coding systems and the use of aggregated surgical data. Studies are therefore limited to smaller selected populations.[117] The majority of evidence has focussed upon the

comparison between endoscopic and open carpal tunnel decompression (CTD) surgery, with rates quoted for short term reoperation have ranged from 0.1% to 2.5%, and overall complication rates potentially as high as 8% in meta-analytic estimates from systematic review.[114-116]

The primary clinical aim of this study was to estimate the incidence of primary CTD surgery and serious post-operative complications, including rates of revision surgery, in adults in the NHS in England.

The primary methodological aim of this study was to appraise the role of administrative secondary care data available in England as a means to determining temporal trends in surgery, and in identifying patients who have a poor outcome.

3.3 Methods

3.3.1 Data source & participants

Using the bespoke HES APC extract linked to ONS mortality records described in Chapter 2.2, a cohort of adult patients undergoing primary CTD surgery was made. Each CTD procedure was treated as an individual event. In order to include only those patients with chronic CTS, any CTD surgeries associated with trauma (e.g., wrist fracture) in the same episode were excluded. This study therefore analysed only on the remaining elective CTD, assuming they were undertaken for chronic CTS.

3.3.2 Validation study

Co-authors: Christian Schnier, Cathy Sudlow, Wee Leon Lam and Lucy Popplewell (UK Biobank); Angela Balkwill, Kirstin Pirie and Akira Wiberg (MWS)

Full details of the methodology of this study are given in Chapter 2.2.3. A list of OPCS procedure and ICD diagnosis codes was generated through multidisciplinary iterative discussion between surgeons, clinical coders, epidemiologists and staff at NHS Digital (Appendix tables A.1 and A.2; discussion group including CS, CS JG, AB). Working alongside members of the UK Biobank core team (CS and CS), participants with the codes of interest in their routinely collected data were identified and anonymized. 2 clinicians for each condition (JL, WLL and LP) then reviewed the anonymized electronic healthcare records using algorithms for a true disease case. Interobserver reliability was determined, and the whole study replicated in Oxford using the anonymized electronic healthcare records of women identified from the Million Women Study (JG, AB, AW). Full results are given in Appendix A . The positive predictive value PPV for CTS using the generated code list was 96% for clinical incident disease; 90% for prevalent disease. Interobserver reliability identified that there was good correlation between the clinical reviewers, with agreement in 90% of cases for CTS (Cohen's kappa 0.79) This work emphasised the need for multidisciplinary discussion to generating a work list of codes to define a true clinical case and the importance of validation prior to analysis. This study suggested that UK secondary care data can identify true cases of CTS and BTOA, with further work needed to externally validate and to further interrogate primary care data sources. This work was published within the Biorxiv pre-print server on 02/03/18 (https://www.biorxiv.org/content/early/2018/03/02/274167). Limitations of this style of validation are discussed in Chapter 2.2.3

3.3.3 Exposures and Outcomes

Exposures and outcomes were defined using previously validated OPCS-4.8 and ICD-10 codes in chapter 2.2.3 and Appendix A (table A.1), and comorbidities were defined using ICD codes given in and Appendix B (tables B.1 and B.2). For the definition of a primary CTD procedure, sensitivity analyses were undertaken in order to differentiate a diagnosis of chronic CTS from that of acute CTS associated with a traumatic injury. In this extract, anyone with a forearm trauma ICD code associated in the same episode of care was excluded (S52), and only those with a CTD code within the first three operation fields were found to be those presenting with chronic CTS.

Exposures were defined as predisposing factors associated with the development of CTS identified from the literature (past medical history of diabetes mellitus, hand osteoarthritis, gout, previous wrist fracture, rheumatoid arthritis, obesity and hypothyroidism).[43, 61, 62, 65, 67, 160-162] Patients were considered to have a past medical history of a condition if a code associated with the condition was found within the hospital episode for CTD, or any previous hospital episode. Charlson Comorbidity Index (CCI) was calculated for each individual over the whole dataset as an overall measure of comorbidity, and Index of Multiple Deprivation (IMD) also used as a potential exposure associated with poor outcome following surgery.[129, 134, 135]

Serious complications resulting in further admission within the HES APC dataset were considered as a measure of outcome from surgery within 30 or 90 days of surgery. The complications investigated were those that form a routine part of our surgical consent process: wound infection or dehiscence, neurovascular or tendon injury, tenosynovitis

requiring surgery. I defined a complication as an appropriate OPCS or ICD code on the same hand as the index CTD (Appendix B table B.3). I defined clinically relevant timeframes for each complication, with reference to the NHS outcome framework.[163] Revision CTD was defined as that occurring at any point during the follow up period and identified using either a) an OPCS code for revision CTD and a previous code for primary CTD on the same hand; b) two primary CTD codes in the same patient on the same hand; c) three or more primary CTD codes in the same individual. For survival analysis and revision incidence rate, where time to event is critical, only those patients defined by criteria a) or b) were included.

Data processing was undertaken as described in Chapter 3.2.6 with minimum follow up set to one day due to the clinical experience of SAEs occurring within a short post-operative time frame.

3.3.4 Statistical Analysis

ONS mid-year population estimates were used to generate age and gender adjusted incidence rates for CTD and revision CTD, with complications calculated with 95% confidence intervals using a Poisson distribution.[164] Complete case analysis was undertaken for these analyses due to the low level of missing data described in Chapter 2.2.5. Laterality was found to be missing in 3.8% (n =32 916) cases; comparison of the demographics of those with and without laterality defined was found to be sufficiently similar to prevent selection bias within the analysis (Appendix B Table B.3)

Time to revision was determined using a Kaplan Meier analysis, and a Fine and Gray model was used to identify the factors associated with revision and complications in order to adjust for the competing risk of mortality over the long follow up period.[165] Cox proportional hazard modelling was used to identify the risk factors for complications of surgery at 90 days, with Schoenfeld residuals used to test the proportional hazards assumption. Age, IMD, CCI and sex were used as adjustment factors within multivariable analysis, with the median category used as the reference variable. Because a non-linear relationship between SAEs and age was found, age was divided into a categorical variable rather than analysing it as a continuous variable.

3.4 Results

3.4.1 Standardised incidence rates

Figure 4.1 describes the data processing details with 885 838 primary CTD surgeries performed in 665 090 patients during the 19-year period. 68% (n=581 645) were performed on female patients, with a median age of 57 years at surgery (IQR 46.9-70.7) (Table 4.1 and Appendix B Table B.4). Overall incidence rate of CTD surgery was 1.10 per 1 000 person years (95% CI 1.02 to 1.17), with a sex specific incidence rate for men of 0.73 per 1 000 person years (95%CI 0.73- 0.74) and 1.47 per 1 000 person years (95%CI 1.47 to 1.48) for women.

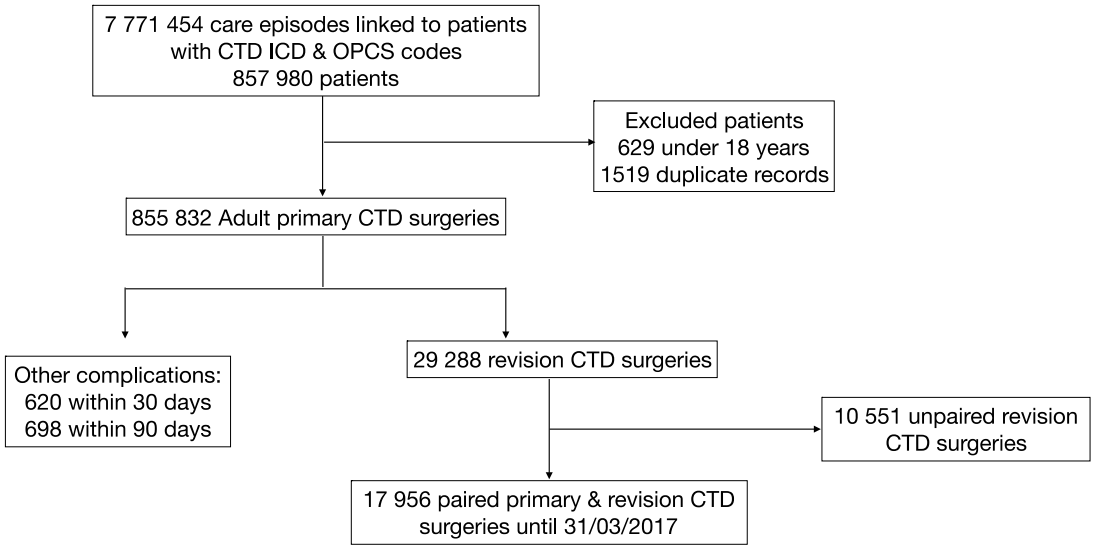


Figure 3.1 Data processing flow chart

Table 3.1 Demographics of included patients

	Primary CTD Number (%)	**Revision CTD or Complication** [a] Number (%)
Sex		
Female	581 645 (67.96)	19 333 (64.58)
Male	273 845 (32.00)	10 600 (35.41)
Missing	343 (0.04)	3 (0.01)
Mean Age (SD; years)	57.9 (15.6)	59.7 (15.6)
IMD decile		
Least deprived 10%	76 234 (8.97)	2 481 (8.29)
Less deprived 10-20%	85 801 (10.10)	2 749 (9.18)
Less deprived 20-30%	87 873 (10.34)	2 992 (9.99)

Less deprived 30-40%	91 842 (10.81)	3 187 (10.65)
Less deprived 40-50%	90 257 (10.62)	3 129 (10.45)
More deprived 10-20%	81 535 (9.60)	3 071 (10.26)
More deprived 20-30%	83 448 (9.82)	3 047 (10.18)
More deprived 30-40%	85 702 (10.09)	3 021 (10.09)
More deprived 40-50%	89 949 (10.59)	3 137 (10.48)
Most deprived 10%	77 114 (9.07)	2 930 (9.79)
Missing	6 077 (0.71)	192 (0.64)
Ethnic group		
Any white background	641 678 (74.97)	24 375 (81.41)
Any Asian background	19 295 (2.26)	701 (2.34)
Any Black background	10 645 (1.24)	472 (1.59)
Any mixed background	2 679 (0.32)	118 (0.39)
Chinese	1 181 (0.14)	25 (0.09)
Any other ethnic group	8 268 (0.96)	262 (0.88)
Not given/not known	172 085 (20.11)	3983 (13.3)
Charlson index		
0	389 351 (45.50)	11 585 (38.70)
1	179 437 (21.00)	6 908 (23.08)
2	97 719 (11.42)	3 709 (12.39)
3-4	98 781 (11.54)	4 027 (13.45)

5+	9544 (10.58)	3 707 (12.38)

3.4.2 Trends in primary surgery

A bimodal distribution was observed in women, with a peak in incidence around the menopause (Figure 3.2) In both sexes there was then a subsequent increase in surgical incidence around UK retirement age, peaking at around 80 years old.

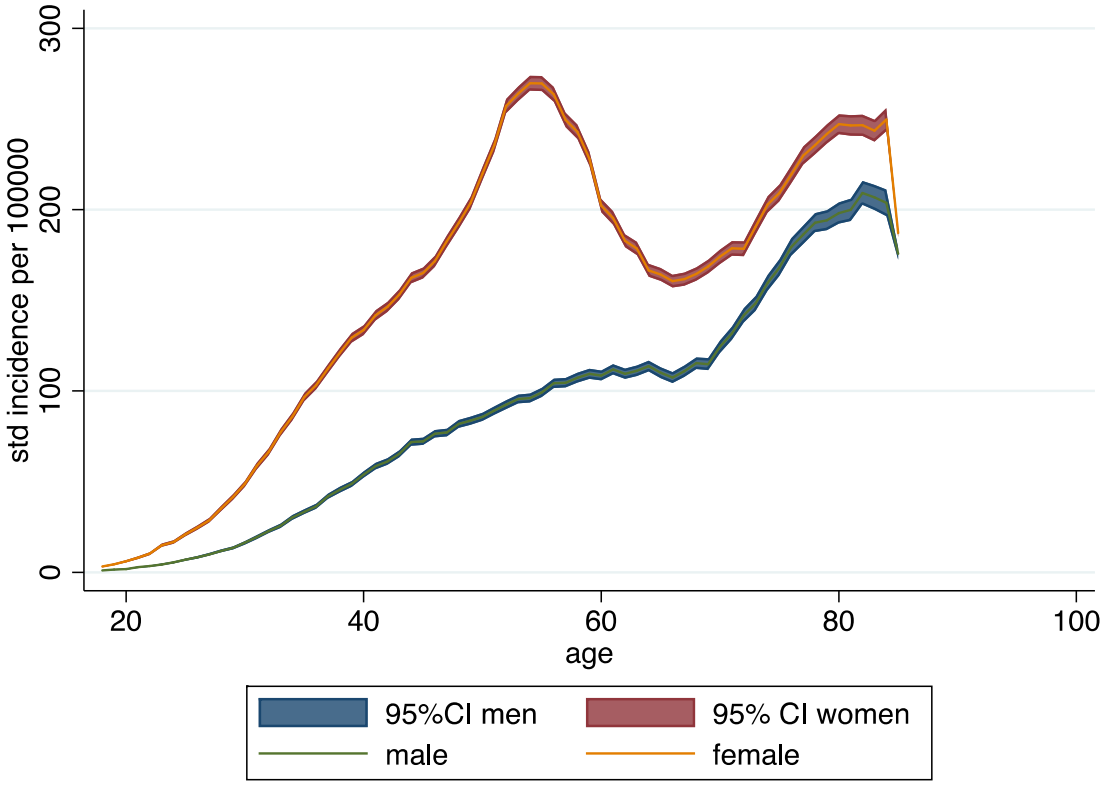


Figure 3.2 Age and sex specific incidence of CTD undertaken in NHS in England, 1998-2017

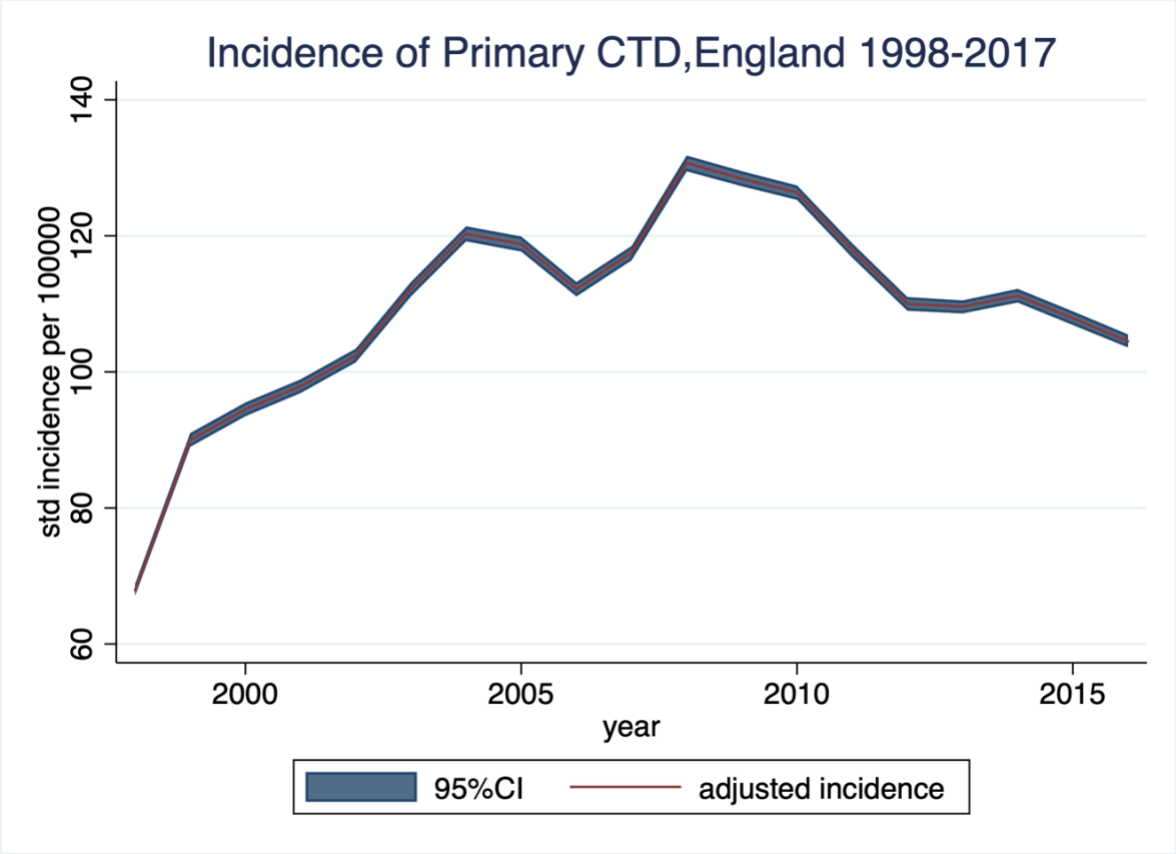


Figure 3.3 Trend in primary CTD surgery, NHS England 1998-2017

3.4.3 Incidence and trends in revision surgery

When including all revision surgeries, including those unpaired with laterality, 29 288 (3.42%) CTDs proceeded to revision. The median follow-up time for all patients was 7.53 years (IQR 3.65 to 12.02), producing an incidence rate of 3.18 per 1000 person years (95% CI 3.13-3.22).

In the 17 956 paired primary and reoperation procedures. A smaller proportion of patients were female, with a younger age than the general cohort (64.8% were female, median age of 60 years (IQR 49 to 74). The median time to reoperation was 351 days (IQR 144 to 966) (Figure 3.4)

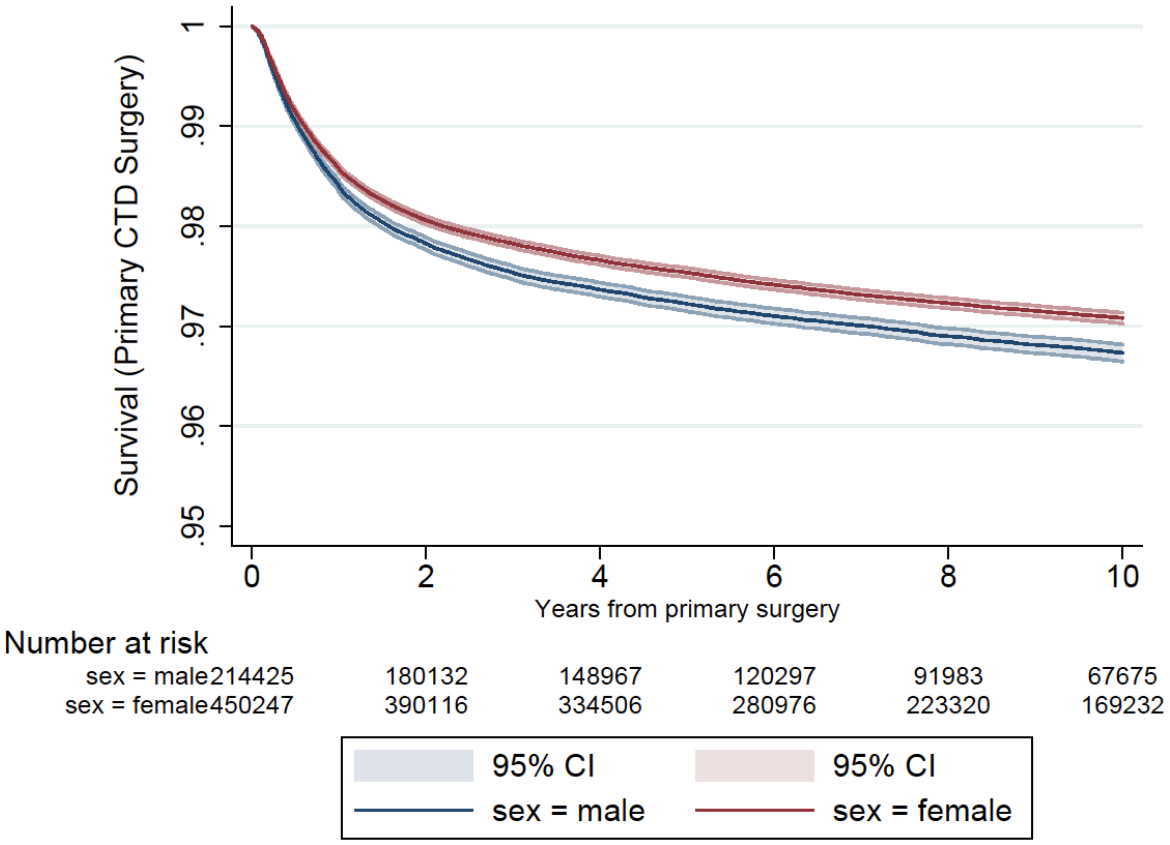


Figure 3.4 Kaplan Meier plot for CTD revision surgery, 10 years following primary CTD

3.4.4 Factors affecting the incidence of revision surgery

Increased risk of revision was associated with male sex (subhazard ratio 1.09 (95% CI 1.06 to 1.13)), increasing comorbidity, increasing age and social deprivation (Table 3.2; Figure 3.5)

Table 3.2 Subhazard ratio (SHR) for risk of revision surgery; crude and adjusted hazard ratio (HR) for risk of other complications

		Total in group	Total revision	Revision Surgery		Total comps	Other Complications[a]	
				Crude SHR[b] (95%CI)	Adjusted SHR[b] (95%CI)		Crude HR[c] (95%CI)	Adjusted HR[c](95%CI)
Sex	Female	581 645	18 968	*1 (reference)*	*1*	375	*1*	*1*
	Male	273 845	10 318	1.11 (1.07 to 1.15)	1.09 (1.06 to 1.13)	289	2.30 (1.73 to 3.06)	2.32 (1.74 to 3.09)
Age group (years)	18-29	19 042	501	0.83 (0.74 to 0.93)	0.85 (0.76 to 0.96)	20	2.09 (1.02 to 4.25)	2.25 (1.10 to 4.62)
	30-39	87 159	2 513	0.96 (0.90 to 1.02)	0.99 (0.93 to 1.05)	64	1.19 (0.72 to 1.94)	1.20 (0.72 to 2.00)
	40-49	164 434	5 515	1.08 (1.03 to 1.13)	1.09 (1.04 to 1.14)	117	0.96 (0.62 to 1.47)	0.98 (0.63 to 1.51)
	50-59	215 441	6 740	*1 (reference)*	*1*	174	*1*	*1*
	60-69	145 162	5 240	1.09 (1.04 to 1.14)	1.05 (1.00 to 1.10)	115	1.08 (0.70 to 1.67)	0.99 (0.64 to 1.53)
	70-79	131 493	4 985	1.13 (1.08 to 1.18)	1.06 (1.01 to 1.12)	104	0.96 (0.61 to 1.53)	0.84 (0.52 to 1.36)
	Over 80	91 465	3 617	1.16 (1.10 to 1.23)	1.09 (1.03 to 1.15)	70	0.64 (0.34 to 1.18)	0.59 (0.31 to 1.11)
Charlson Index	0	389 351	11 336	*1 (reference)*	*1*	256	*1*	*1*
	1	179 437	6 762	1.21 (1.17 to 1.26)	1.22 (1.18 to 1.28)	149	0.91 (0.62 to 1.33)	0.98 (0.67 to 1.44)
	2	97 719	3 617	1.15 (1.09 to 1.20)	1.17 (1.11 to 1.23)	93	0.94 (0.58 to 1.51)	1.06 (0.65 to 1.73)
	3-4	98 781	3 952	1.25 (1.19 to 1.31)	1.26 (1.20 to 1.33)	77	0.75 (0.45 to 1.27)	0.86 (0.50 to 1.48)
	5+	90 544	3 621	1.22 (1.17 to 1.28)	1.25 (1.19 to 1.32)	89	1.32 (0.86 to 2.03)	1.48 (0.31 to 1.11)
Indices of Multiple Deprivation (deciles)	Least deprived 10%	76 234	2 416	*1 (reference)*	*1*	65	1	1
	Less deprived 10-20%	85 801	2 694	1.03 (0.96 to 1.11)	1.03 (0.96 to 1.11)	55	0.57 (0.27 to 1.17)	0.55 (0.27 to 1.14)
	Less deprived 20-30%	87 873	2 925	1.06 (0.99 to 1.14)	1.06 (0.99 to 1.14)	69	1.01 (0.55 to 1.87)	0.99 (0.53 to 1.83)
	Less deprived 30-40%	91 842	3 115	1.09 (1.02 to 1.17)	1.09 (1.02 to 1.17)	75	1.06 (0.58 to 1.94)	1.03 (0.57 to 1.89)
	Less deprived 40-50%	90 257	3 061	1.07 (1.00 to 1.14)	1.07 (1.00 to 1.15)	69	1.03 (0.56 to 1.89)	1.00 (0.55 to 1.84)
	More deprived 10-20%	81 535	3 006	1.20 (1.12 to 1.29)	1.20 (1.12 to 1.29)	67	1.10 (0.60 to 2.04)	1.05 (0.57 to 1.95)
	More deprived 20-30%	83 448	2 983	1.15 (1.07 to 1.23)	1.14 (1.05 to 1.20)	65	0.78 (0.40 to 1.52)	0.75 (0.38 to 1.46)
	More deprived 30-40%	85 702	2 963	1.13 (1.05 to 1.21)	1.12 (1.05 to 1.20)	61	0.85 (0.45 to 1.62)	0.82 (0.43 to 1.56)
	More deprived 40-50%	89 949	3 062	1.11 (1.04 to 1.19)	1.10 (1.03 to 1.18)	77	0.99 (0.54 to 1.83)	0.96 (0.52 to 1.77)
	Most deprived 10%	77 114	2 876	1.19 (1.11 to 1.27)	1.18 (1.10 to 1.27)	55	0.69 (0.34 to 1.39)	0.65 (0.32 to 1.33)

[a]other complications (wound infection, wound dehiscence, nerve injury, tendon injury) at 90 days

[b]Fine and Gray model of competing risks

[c] Cox proportional hazards model; comps= complications

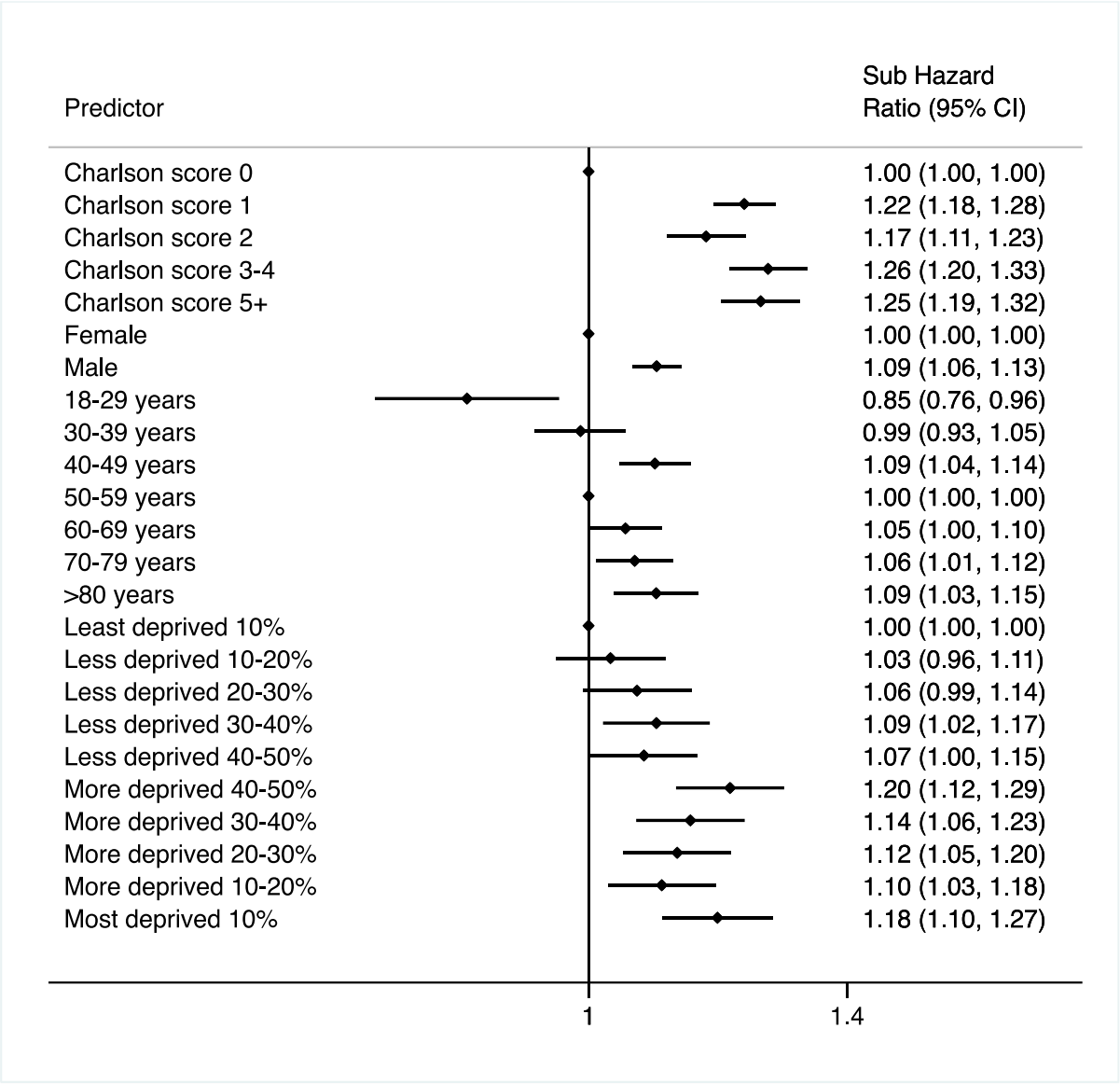


Figure 3.5 Forest plot of adjusted subhazard ratios for reoperation at any time post operatively, accounting for the competing risk of mortality.

3.4.5 Incidence of serious adverse events

Table 3.3 shows the incidence of complications following CTD surgery, with all complications below 0.1%. Local complication occurred in 0.07% (95% CI 0.067 to 0.078; n=620) cases within 30 days and in 0.08% (95%CI 0.076 to 0.088; n=698) cases within 90 postoperative days. The highest incidence at 90 days was seen in wound dehiscence and

tendon injury (0.03%; 95%CI wound dehiscence (0·029 to 0·037; n=282); 95% CI tendon injury (0·025 to 0·031; n=285)).

Table 3.3 Complications sustained within 30 and 90 Days of CTD

	Time	Total cases (N)	% (95% CI)
Wound dehiscence	Within 30 days	259	0.03 (0.027 to 0.034)
	Within 90 days	282	0.03 (0.029 to 0.037)
Wound infection	Within 30 days	32	0.004 (0.0026 to 0.0053)
	Within 90 days	43	0.005 (0.0037 to 0.0068)
Tendon injury	Within 30 days	241	0.03 (0.025 to 0.031)
	Within 90 days	285	0.03 (0.030 to 0.037)
Neurovascular injury	Within 30 days	88	0.01 (0.0083 to 0.013)
Any complication	Within 30 days	620	0.07 (0.067 to 0.078)
	Within 90 days	698	0.08 (0.076 to 0.088)

3.4.6 Factors affecting the incidence of SAEs

Again, male sex was associated with an increased risk of adverse outcome, in particular associated with SAEs aside from revision surgery. CCI and deprivation were not associated with SAEs, but those who were younger were over twice as likely to develop a local wound complication (Figure 3.6).

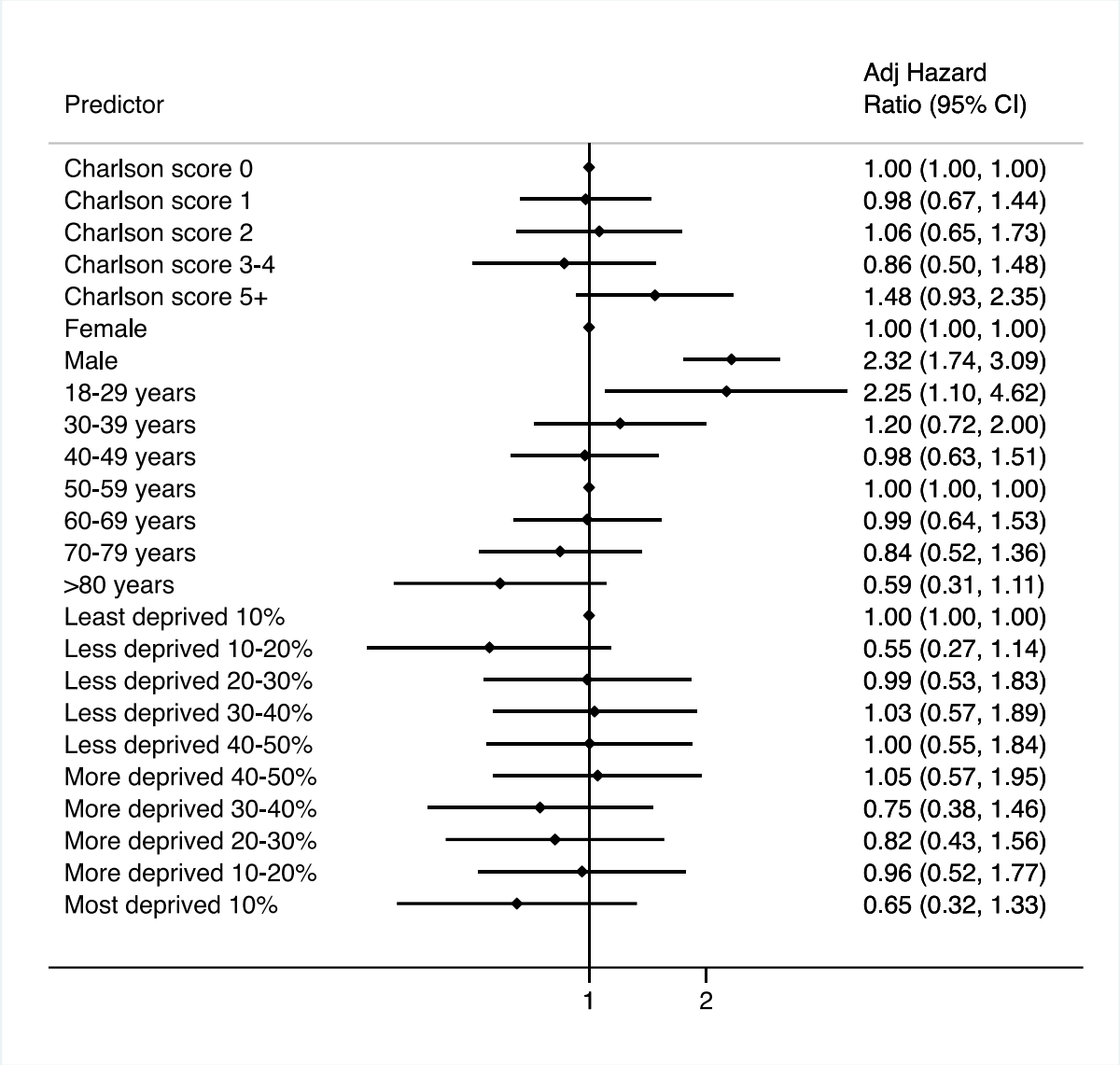


Figure 3.6. Forest plot of adjusted hazard ratios for local complications within 90 days of surgery. (see table 3.2 for absolute values)

3.5 Discussion

3.5.1 Key findings

This large retrospective cohort study within a nationalised healthcare system identifies the incidence of CTD surgery in the English NHS, and the incidence of both revision surgery and SAEs in a general population. A low rate of revision surgery at 3.4% and complications at 0.08% was identified over a long longitudinal follow up. Increased risk of revision carpal

tunnel decompression was associated with male sex, increasing comorbidity, age and social deprivation, with male sex and younger age associated with local serious complications. Methodologically, this study identifies the ability of HES APC to generate demographic and temporal trends in surgery for chronic CTS, with its strength being in the longitudinal follow up it contains. Revision procedures and serious complications were able to be identified in the data if laterality was present, and if the event was recorded as requiring a hospital admission. For revision surgery, this is very likely to be undertaken in a secondary care or HES APC remunerated minor operations setting, but the need for admission is a significant caveat for identification of complications after a local anaesthetic procedure. Finally, this study identified that it was possible to obtain and directly data manage a data cut from HES APC to generate a bespoke extract for a surgical procedure, based upon a validated set of OPCS and ICD codes without a wider technical support structure.

3.5.2 Strengths and Limitations

This study includes all marginal patient subgroups and reflects the public workload across an entire country, including the ability to identify revision procedures undertaken another hospital within the NHS. The low rate of private healthcare within England also enables better data capture nationally of activity within the general population, with few patients requesting their data to be removed from HES APC, and low overall levels of emigration in England.[130, 166, 167]

Exposures and complications reported in this study are necessarily defined by an episode in secondary care, limiting our results to those that are more clinically relevant. However, they

constitute the complications routinely discussed as part of the consent process with patients, and therefore this study can further inform future shared clinical decision-making discussions for individual patients, in addition to those surrounding commissioning of services for populations.

The ability to censor due to the link to national mortality data provides a longer term follow up after surgery that can be difficult in individual electronic health care records or within private insurance data. Focused on secondary care and surgical outcome, we provide generalizable results with a level of detail and external validity not possible from primary care data or private insurers. The wealth of individualized information included in each hospital episode of care also enables acute CTS to be excluded which is not possible in other routinely collected datasets with less granularity, or when using aggregated data platforms. The Hospital Episode Statistics dataset was originally designed to calculate costs within the NHS rather than for research, and therefore the limitations of the included data must be acknowledged. Data regarding some risk factors for CTD such as occupation, or conservative treatment given in primary care or outpatient setting cannot be observed, and others such as obesity are likely to be under-reported. This work has been more suitably undertaken in primary care or workforce settings.[50, 51, 162] As the method of reimbursement, HES APC data has the potential bias of over-reporting of comorbidity and complications, in order to increase remuneration. In contrast, clinical datasets may suffer from under-reporting of adverse events, and publication bias may exacerbate this problem. Our data are therefore likely to represent upper estimates for these parameters, but despite this we report a very low rate of complications.

3.5.3 Comparison to other studies

It shows that the incidence of CTD surgery in the NHS in England has been low over the last 18 years compared to the prevalence of CTS quoted in the literature, albeit from smaller studies.[46, 50, 168] Vasiliadis *et al.* identified 26 studies of complications following CTD surgery, with a predominant focus upon endoscopic versus open techniques in a Cochrane review.[169] Reoperation was quoted at around 2.5%, with major complications reported as less than 1% within their meta-analysis (neurovascular or tendon injury) and minor complications (scar complaints, infection, pain) at 10.2%. Within my study, the revision rate appears comparable, and I report a lower rate of major complications. Post-operative infection rates found in this study are also substantially lower than those described in the literature in smaller or single centre cohorts.[115] Minor complications as discussed within the Cochrane review are outside of the remit of this study, as HES APC will only register complications requiring a procedure or a minimum of a day case admission. This may explain why lower rates of major complications are also found and should be remembered as a limitation of HES data (Chapter 2.2.7).

3.5.4 Future research

Routine collection of patient reported outcome measures (PROMS) have revolutionised other areas of orthopaedic surgery to enable surgical provision to remain patient focused when undertaking commissioning and health economic assessments. Hand surgery has promoted collection of national PROMS data from a professional perspective, but this is yet to be truly representative of NHS workload.[21] Whilst complication rates and rates of surgery are vital for informing outcome data, further work to undertake a cost effectiveness analysis

based upon mandatory PROMS collection would be valuable in order to assess the comparative cost-effectiveness of surgery in the treatment of CTS. The value of the UK Hand Registry will be appraised in Chapter 5, and future work could also focus on additional collection of PROMS for CTD within this registry to drive this analysis.

4. Administrative data (Part 2): HES APC – surgical subtypes

Trends in incidence of and risks of serious adverse events and further procedures following intervention for Base of Thumb Osteoarthritis, Hospital Episode Statistics for England 1998-2017[†]

Contributions: All work and data in this chapter was curated, designed, analysed and interpreted by myself apart from assistance within validation studies. In section 4.3.2.1 Mr Wee Leon Lam and Dr Lucy Popplewell assisted as second reviewers of patient notes with data extract generated by Dr Christian Schnier in UK Biobank and senior advice from Prof Cathy Sudlow; Mr Akira Wiberg assisted as the second reviewer of patient notes with data extract for the validation study generated by Dr Angela Balkwill and Dr Kirstin Pirie for MWS. In section 4.3.2.2.1 Miss Michelle Spiteri, Miss Abigail Shaw and Mr Ben Dean assisted as reviewers of patients notes, and in section 4.3.2.2.2 Mr Nicholas Riley and Mr Mark Mikhail assisted as reviewers of patients notes. With thanks to Mr Richard Craig for his co-curation of the raw HES data, and senior advice from Prof Jonny Rees.

[†] Parts of this content has been published in Rheumatology (Oxf) and presented at the BSSH-IFSSH Joint meeting, November 2019. 170. Lane JCE, Craig RS, Rees JL, Gardiner MD, Shaw AV, Spiteri M, et al. Low rate of subsequent surgery and serious complications following intra-articular steroid injection for base of thumb osteoarthritis: national cohort analysis. Rheumatology (Oxford). 2021.

4.1 Summary

Part one of this large national cohort found only 50% (n=9651/19 120) had any form of intervention after their first intraarticular steroid injection for BTOA, with only 22% (n=428/19 120) proceeding to surgery during the follow up period. Further interventions mostly occurred within a year of the injection. Very low rates of SAEs were found after intra-articular injection or BTOA surgery, and the injection did not increase post-operative complications if the individual proceeded to surgery after injection.

The second part of this chapter focusses on the role of surgery for BTOA. The primary surgery undertaken in the NHS in England is trapeziectomy, with an increasing trend over the 19 year period studied. The overall rate of revision intervention was low at 1.39% (n=599/43 076), but the risk was twice as high for those undergoing arthroplasty of arthrodesis. Overall complication rates following surgery were less than 0.3% (n=87/ 43 076) for local complications and less than 0.6% (n=250/ 43 076) for systemic complications within the first 90 days post operatively.

4.2 Introduction

Intra-articular steroid injection and surgery for BTOA are a common treatment despite a paucity of evidence describing its efficacy and safety.[85] A systematic review noted that whilst RCTs had been undertaken, the evidence supporting use remains heterogenous and unclear. Some studies have suggested that at least one third of patients require surgery following injection, and there is little available national level data with long term follow up.[86]

Similarly, the evidence is unclear as to whether patients undergoing intra-articular injection have increased complications if they progress to surgery. Work by Giladi *et al.* has suggested a high rate of complications for those undergoing BTOA surgery after intraarticular injection, but this is in contrast with research into the role of intra-articular steroid injections in other anatomical locations, that have suggested no increase in post-operative surgical site infection.[87-89]

Current evidence surrounding the safety of surgery for BTOA is confined to small single centre studies in routine clinical practice. A variety of techniques can be employed, but it is thought that most surgery undertaken is either simple trapeziectomy or trapeziectomy with ligament reconstruction and tendon interposition (LRTI).[90-92] Like other areas of orthopaedic surgery, there is an increasing use of arthroplasty to treat BTOA with a variety of implants emerging onto the market. [99-103, 105, 171] Studies predominantly compare two techniques, with few comparing multiple surgical subtypes. Evaluation of surgical techniques in a recent Cochrane review was unable to identify superiority of one technique with a high risk of bias.[106] However, an elevated risk of complication has been suggested with LRTI and arthroplasty compared to trapeziectomy alone, some suggesting complication rates up to 35%. [97, 112, 118]

In the first part of this study, the primary clinical aim was to establish the incidence of intraarticular BTOA steroid injections undertaken in secondary care in England, and the trends over time. The study aimed to identify the incidence of further procedures after injection. The secondary aim was to determine the complications following injection, and if there were identifiable factors associated with progression to further intervention or

complications. Finally, I aimed to determine if preoperative BTOA injection was associated with an increased risk of serious surgical site infection, as identified in the HES APC dataset.

In the second part of this study the primary aim was to determine the incidence of surgical subtypes undertaken in England for BTOA, and the trends over time. The work aimed to identify the rate of revision surgery, local and systemic complications following BTOA surgery, and if it was possible to identify factors associated with these adverse outcomes.

The methodological aims of this chapter were to build upon the work undertaken in chapter 3. BTOA is more nuanced in its OPCS and ICD coding than CTS, and includes a large variety of surgical subtypes. This chapter therefore aimed to test the robustness of HES in its ability to identify more complicated surgical procedures. In addition, the potential to identify BTOA injections recorded in HES admitted patient care offered the opportunity to explore how inclusion bias may impact recording of such interventions. As routinely collected data in secondary outpatient care remains largely unused in research exploring trends in interventions in clinic, it appeared pertinent to identify if HES APC could be used to identify musculoskeletal injections, particularly those that are increasingly radiologically-guided.

4.3 Methods

4.3.1 Data source & participants

2 extracts were generated from the bespoke pseudonymised HES APC dataset described in Chapter 2.2. All patients aged over 18 years were included and divided into a cohort of those who had undergone primary BTOA intraarticular injection and primary BTOA surgery.

As with the analysis in Chapter 3, patients who had a code for trauma within the same episode were excluded due define the cohort as those with chronic BTOA only.

4.3.2 Exposures and Outcomes

Exposures were defined using the validated code lists given in Appendix A table A.2 that were generated through the validation study described in Chapter 2.2.3 and 3.3.2. Procedures were identified using OPCS-4.8 classification for interventions and diagnoses using ICD version 10.[132, 133]

4.3.2 Validation studies

4.3.2.1 Main exposure identification- BTOA

Co-authors: Christian Schnier, Cathy Sudlow, Wee Leon Lam and Lucy Popplewell (UK Biobank); Angela Balkwill, Kirstin Pirie and Akira Wiberg (MWS)

In the main validation study undertaken in UK Biobank and replicated in Million Women Study described earlier, the positive predictive value PPV for incident BTOA was 81%, prevalent disease 56%. Interobserver reliability identified that there was good correlation between the clinical reviewers, with agreement in 98% for BTOA (Cohen's kappa 0.96).

4.3.2.2 BTOA subgroups

Two further studies were run locally in Oxford University Hospitals (OUH) NHS Foundation trust to identify if HES APC could identify BTOA intra-articular injections and surgical subtypes undertaken for BTOA. For both BTOA injection and BTOA surgical subtypes, a year

cohort of patients were identified from electronic health records, and their records independently appraised by two clinicians to determine the PPV of the code list generated.

4.3.2.2.1 BTOA injection

Co-authors Michelle Spiteri, Abigail Shaw and Ben Dean

This represented a sample of 300 BTOA injections and 104 surgical procedures. Of particular interest was the mode of delivery of BTOA injections likely to be included in HES APC, since BTOA injections were traditionally delivered in outpatient clinics that would not be registered within HES APC. In the OUH sample, patients with clinical coding presented to HES APC had undergone injections in theatre, in specialist outpatient clinic delivered by hand surgeons and rheumatologists, and within the radiology department as image guided injections coded as a day case procedure. A PPV of 85.8% was identified in this study.

4.3.2.2.2 BTOA surgery subgroups

Co-authors Mark Mikhail and Nicholas Riley

A year of BTOA surgery undertaken in OUH represented 104 surgical cases, and the mix of surgical procedures undertaken reflected a similar pattern to that seen in the final analysis at a national level with the predominant procedure being simple trapeziectomy. The PPV identified was 99%.

4.3.4 Covariates

IMD deciles generated by geographical location within HES APC were used to determine socioeconomic status.[129] Ethnicity was defined by aggregating terms generated by NHS

Digital in order to prevent secondary disclosure of data.[172] Charlson Comorbidity Index (CCI) as a global indicator of comorbidity was generated from prior HES APC episodes within the extract itself using the STATA *Charlson* function. [134, 135] Incidence of conditions identified in the literature as associated with the pathogenesis of BTOA were also determined from prior HES APC episodes in the extract using OPCS and ICD codes (Appendix C Table C.1). This included a history of carpal tunnel syndrome or carpal tunnel decompression, knee osteoarthritis, 'generalised' osteoarthritis, rheumatoid arthritis, distal radius fracture and oophorectomy.

4.3.4.1 'Further procedure'

For BTOA injection, this was defined into two groups- those undergoing repeat intra-articular steroid injection, and those undergoing surgery. For the BTOA surgery analysis, this was remained as one group, including revision surgery and BTOA injection, as patients undergoing BTOA injection in the same hand post-surgery were considered to have recalcitrant symptoms by the clinical authors. Further procedure could occur at any point in follow up, within the minimum follow up being one day due to the possibility of presentation with complications shortly after intervention.

As was described in chapter 3, two methods were used to identify further procedure.

1. To generate a 'worst case' scenario percentage of cases proceeding to further intervention, any patient who had three or more episodes with BTOA injection or surgery codes were included. Laterality was not an inclusion criterion since three episodes indicated that one hand had undergone two procedures, but patients missing laterality could not be included in further analysis

2. To identify time to further procedure and revision surgery, to produce an incidence rate of further procedure and to investigate factors associated with further procedure, only patients with two linked episodes with laterality matching (i.e., identifying the same hand) were used.

4.3.4.2 Complications

Complications were identified within 30 and 90 days of intervention in the data extract to align with the NHS quality outcomes framework dashboard and be comparable to available evidence for other procedures.[163, 173-175] The minimum follow up for complications was also set at one day to align with the clinical experience of patients presenting within this timeframe.

4.3.4.3 Injection

Local complications of surgical site infection (as defined by wound dehiscence or debridement), septic arthritis, neurovascular or tendon injury were identified (Appendix C Table C.2).

4.3.4.4 BTOA surgery

As it is current practice in the UK for patients to undergo BTOA surgery under general anaesthetic, local and systemic complications were identified post operatively for the BTOA surgical cohort. In addition to the local complications described for the BTOA injection cohort, the systemic complications identified included stroke, acute myocardial infarction, venous thromboembolic disease, respiratory tract infection, acute renal failure and urinary tract infection (Appendix C Table C.3).

4.3.5 Statistical Analysis

ONS mid-year population estimates were again used to calculate the incidence of primary BTOA injection or surgery, to enable comparison of trends over time with other musculoskeletal conditions.[164] 95% confidence intervals were calculated using a Poisson distribution. For the BTOA injection cohort, laterality code was missing in 6.2% (n=1107); comparison of demographics of those with and without laterality present within their records demonstrated that the patients were comparable (Appendix C Table C.4). For the BTOA surgery cohort, laterality was missing in 16.2% (n=7004) of cases, but comparison of demographics again showed no difference in baseline characteristics of those with and without laterality as a potential source of bias (Appendix C Table C5). Complete case analysis was therefore undertaken without imputation.

The trend in time to further procedure was identified by Kaplan Meier analysis. A Fine and Gray adjustment accounting for the competing risk of mortality was undertaken to investigate the factors associated with further intervention due to the potentially long follow up period included.[165] This produced a both a crude subhazard ratio and an adjusted subhazard ratio through multivariable regression analysis was employed adjusting for sex, age, socioeconomic status (as per IMD decile) and comorbidity (CCI). To identify the factors associated with post intervention complications, a multivariable cox proportional hazards model was used. As complications were identified within 90 days of intervention, it was considered unnecessary to adjust for the competing risk of mortality. Schoenfeld residuals were used to test the proportional hazards assumption. For both the primary BTOA injection

and primary BTOA surgery cohort, age did not have a linear relationship with further procedure and was therefore categorised. The median age category was used as the reference category. In the BTOA surgery analysis, the risk of serious adverse event was of particular interest when divided by surgical subtype. However, due to the positively skewed age distribution of patients, regression analysis was undertaken in patients over 40 years only and was not undertaken for those undergoing partial primary trapeziectomy due to a lack of patients in this subgroup. To investigate the impact of surgical subtype upon the risk of adverse outcome, a sensitivity analysis of the risk of further intervention was compared to that of simple trapeziectomy, in addition to each subgroup within its own analysis adjusting for sex, age, socioeconomic status and comorbidity. This was undertaken in order to assess the confounding by indication within the multivariable model where surgical subtype was used as an adjustment variable.

4.4 Results- BTOA injection

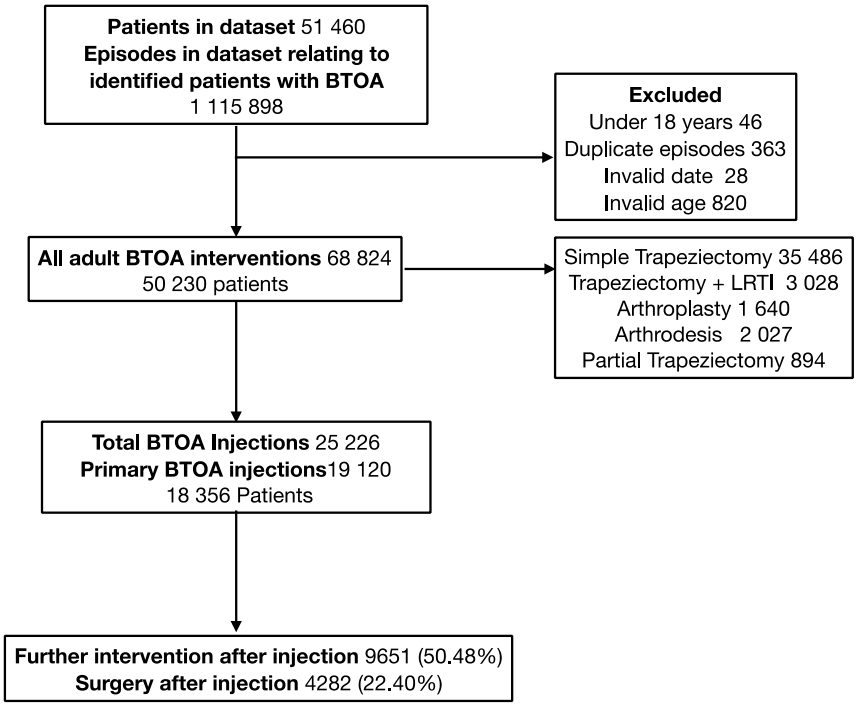


Figure 4.1 Data management flow chart, primary BTOA injection cohort.

4.4.1 Trends in primary BTOA injection

Over the 19 year period, 19120 injections were included in 18356 patients (Figure 4.1). 50.48% (n=9651) went on to receive a further intervention, and 22.40% (n=4282) proceeded to surgery. Table 4.1 gives the baseline demographics of the whole cohort, and those undergoing further intervention or surgery. The majority of patients were female and in the seventh decade of life when they underwent primary BTOA injection. Overall, patients had few concurrent comorbidities, with an even spread of patients throughout the socioeconomic strata. Patients predominantly identified themselves as being of white heritage. When considering the age and sex adjusted incidence of BTOA injections, there was a peak in injections given around perimenopausal age in women that was not seen in the same age range in men (Figure 4.2).

The median follow up time was 5.0 years (IQR 2.2-8.8). Less than one percent of patients had less than 30 days of follow up without a censoring event due to undergoing their injection at the end of the time period in early 2017 (n= 128; 0.67%) and less than two percent had less than 90 days follow up (n=351; 1.40%).

Table 4.1 Baseline characteristics of patients undergoing BTOA injection, any further BTOA intervention or surgical intervention for BTOA following primary injection.

	All injection patients Freq (%)	**Any intervention after 1st injection**	**Surgery after 1st injection**
Sex			
Male	4 492 (23.4)	2 514 (22.3)	953 (22.3)
Female	14 624 (76.5)	7 497 (77.7)	3 325 (77.7)
Missing	<7*	0	<7*
Age category			
18-29	49 (0.3)	<7*	<7*
30-39	280 (1.5)	70 (0.7)	23 (0.5)
40-49	1797 (9.4)	804 (8.3)	369 (8.6)
50-59	5975 (31.3)	3051 (31.6)	1443 (33.7)
60-69	6490 (34.0)	3534 (36.6)	1618 (37.8)
70-79	3486 (18.3)	1785 (18.5)	698 (16.3)
>80	1022 (5.4)	398 (4.1)	123 (2.9)
Missing	21 (0.1)	<7*	<7*
IMD decile			
Least deprived 10%	1651 (8.6)	911 (9.4)	397 (9.3)
Less deprived 10-20%	1805 (9.4)	987 (10.2)	394 (9.2)
Less deprived 20-30%	2119 (11.1)	1033 (10.7)	458 (10.7)
Less deprived 30-40%	2179 (11.4)	1069 (11.1)	468 (10.9)
Less deprived 40-50%	2030 (10.6)	1001 (10.4)	437 (10.2)
More deprived 10-20%	1760 (9.2)	894 (9.3)	394 (9.2)
More deprived 20-30%	1902 (10.0)	918 (9.5)	434 (10.1)
More deprived 30-40%	1844 (9.6)	932 (9.7)	421 (9.9)
More deprived 40-50%	1988 (10.4)	1027 (10.6)	466 (10.9)
Most deprived 10%	1726 (9.0)	836 (8.7)	381 (8.9)

Missing	116 (0.6)	43 (0.5)	28 (0.7)
Ethnic group			
Any white background	16018 (83.8)	8700 (90.2)	3866 (90.4)
Any Asian background	354 (1.85)	140 (1.5)	50 (1.2)
Any Black background	70 (0.4)	22 (0.2)	13 (0.3)
Any mixed background	41 (0.2)	9 (0.1)	<7*
Chinese	16 (0.1)	11 (0.1)	<7*
Any other ethnic group	96 (0.5)	33 (0.3)	11 (0.3)
Not stated	2233 (11.7)	659 (6.8)	268 (6.3)
Not known	292 (1.0)	77 (0.8)	28 (0.7)
Charlson index			
0	7 881 (41.2)	4139 (42.9)	1 966 (46.0)
1	4486 (23.5)	2474 (25.6)	1 078 (25.2)
2	2 535 (13.3)	1230 (12.7)	523 (12.2)
3	1 538 (8.0)	738 (7.7)	306 (7.2)
4	836 (4.4)	361 (3.7)	128 (3.0)
>=5	1844 (9.6)	709 (7.4)	277 (7.4)
Comorbidities			
Carpal Tunnel Syndrome	2123	1107	550
Knee Osteoarthritis	2258	1155	515
General Osteoarthritis	4102	2092	804
Rheumatoid Arthritis	142	30	<7*
Wrist Fracture	110	36	17
Oophorectomy	661	380	185
*Numbers less than 7 suppressed in line with NHS Digital disclosure control guidelines- percentages of other groups rounded to prevent secondary disclosure of data [172]			

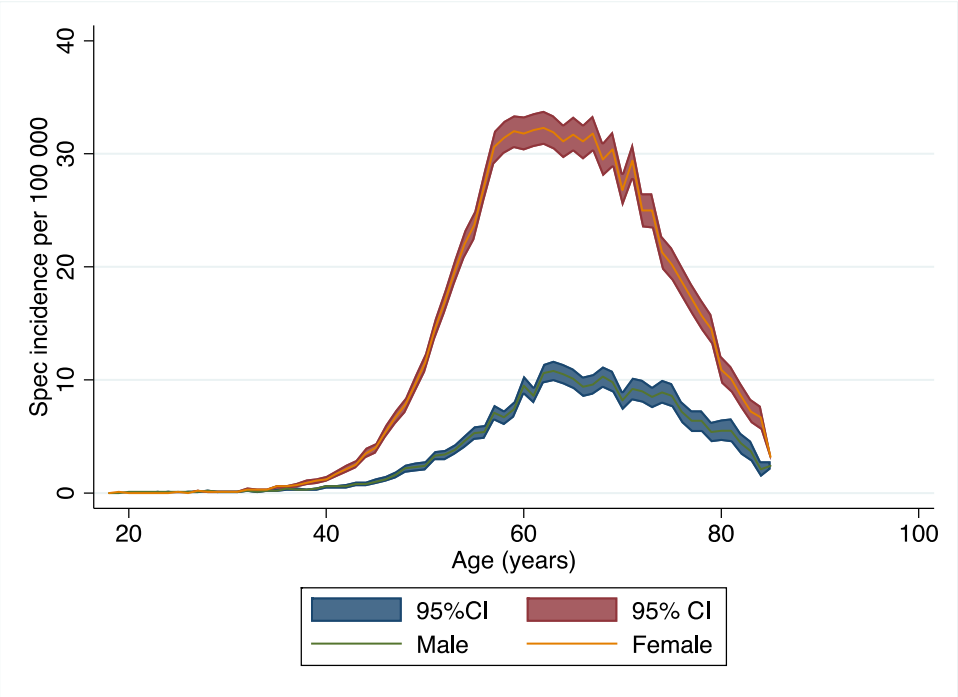


Figure 4.2 Age and sex specific incidence of primary BTOA injections, England, 1998-2017.

4.4.2 Incidence and trends in further procedures- BTOA injection

The incidence rate of any further procedure was 66.7 per 1000 person years, (95% CI (65.06-68.41)) and the incidence of surgery following BTOA injection was 22.3 per 1000 person years (95% CI (21.51 to 23.19)). The majority of further interventions occurred within the first two years post injection, with the median time to further procedure being 412 days (IQR 110-1945) (Figures 4.3a and 4.3b). If patients proceeded to further intervention, the intervention undertaken is expressed within the sunburst plot in Figure 4.4. The inner ring represents the primary BTOA injection cohort, with outer ring identifying the secondary procedures undertaken. Nearly half of all primary injections did not have a further procedure within the follow up period, with half of those undergoing a further procedure

undergoing repeat injection. Of those who underwent surgery, the majority underwent simple trapeziectomy.

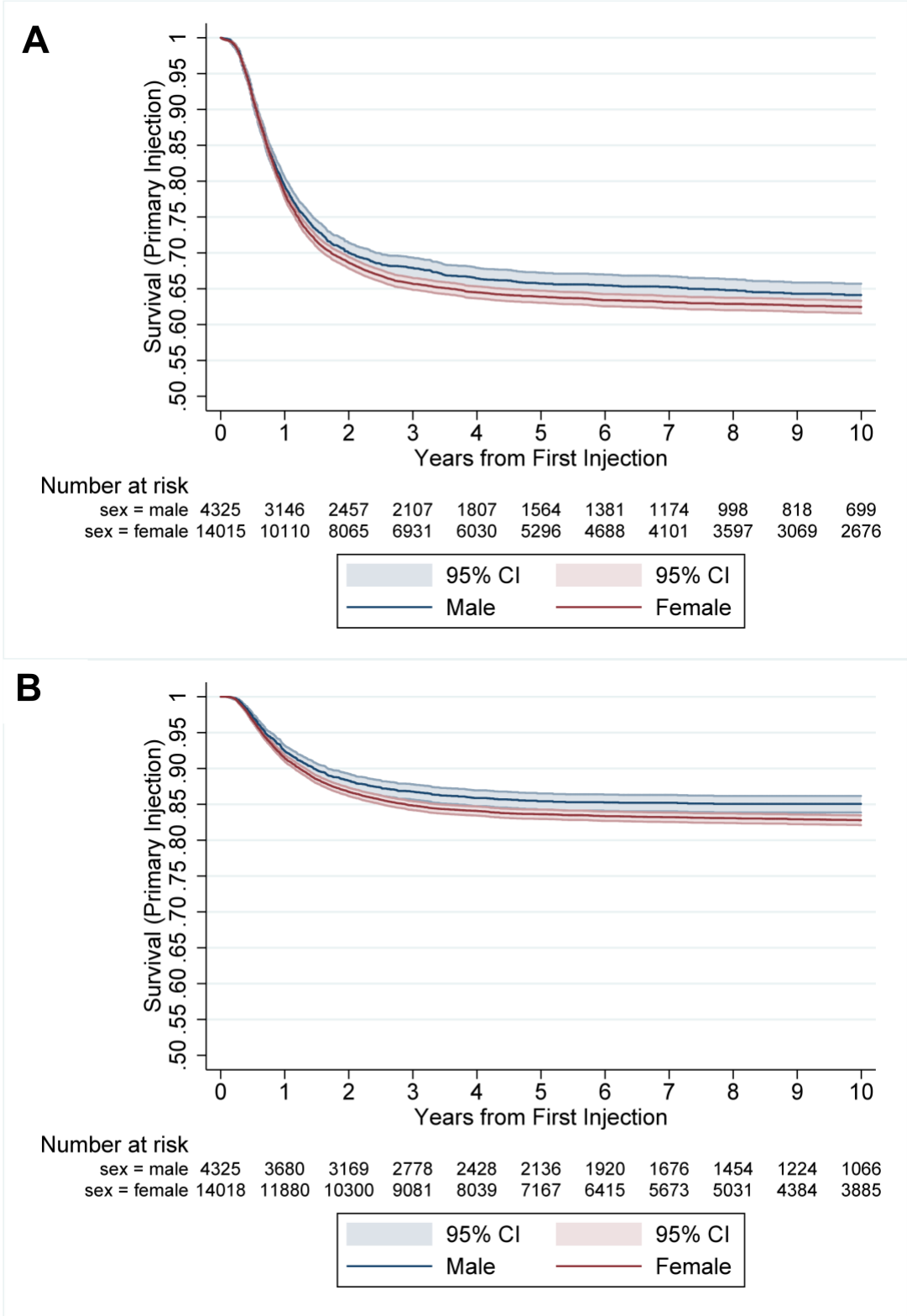


Figure 4.3A and B. Kaplan Meier plots identifying rate of A) any further intervention and B) surgery following primary BTOA injection.

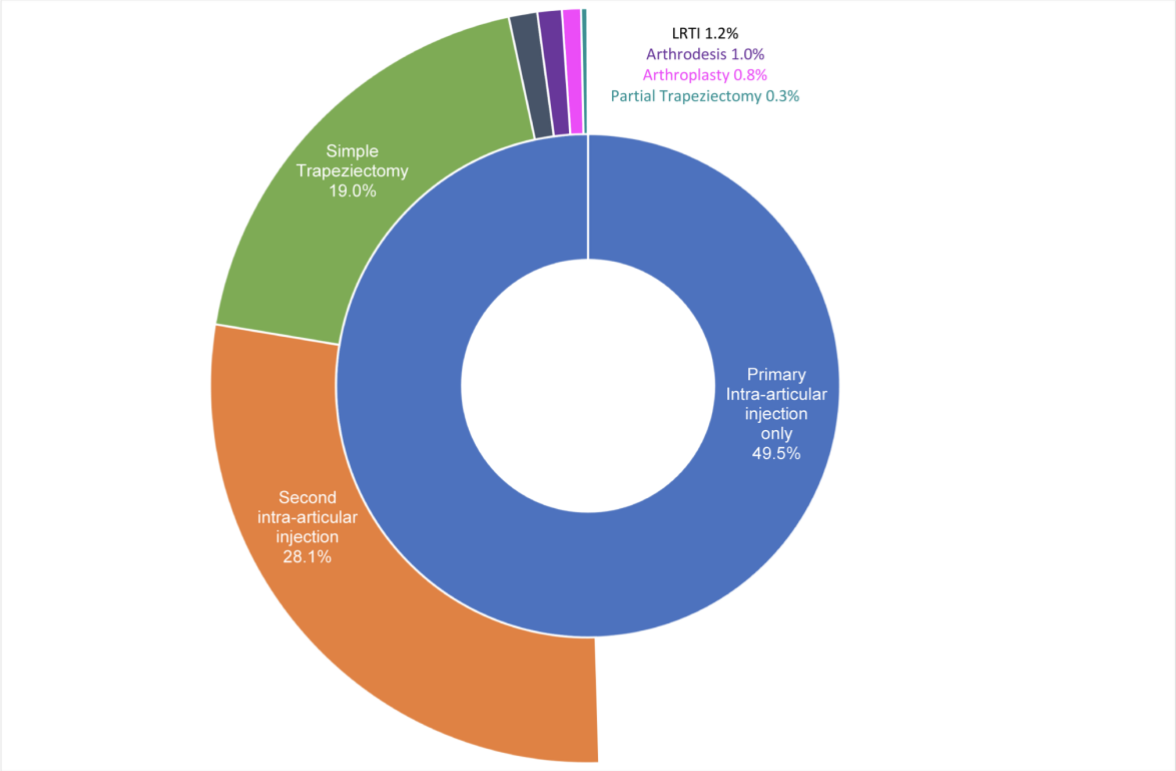


Figure 4.4 Sunburst plot displaying further procedures undertaken following primary BTOA injection.

4.4.4 Factors affecting the incidence of further procedures-BTOA injection

Results of both the crude and multivariable analysis adjusted for age, sex, CCI and IMD are given in Table 4.2. Within the univariable analysis, there was a borderline increased risk of further procedure associated with female sex, which was not maintained within the multivariable analysis. Patients who were in the age categories at the extremes of the range were found to have a reduced risk of further intervention in both univariable and multivariable analysis. There was also a reduced incidence of further procedures seen in those with increasing numbers of comorbidities, as shown by the stepwise reduction in risk of further procedure with increasing CCI score. There appeared to be no association with socioeconomic status. Figure 4.5 shows the results from the multivariable analysis.

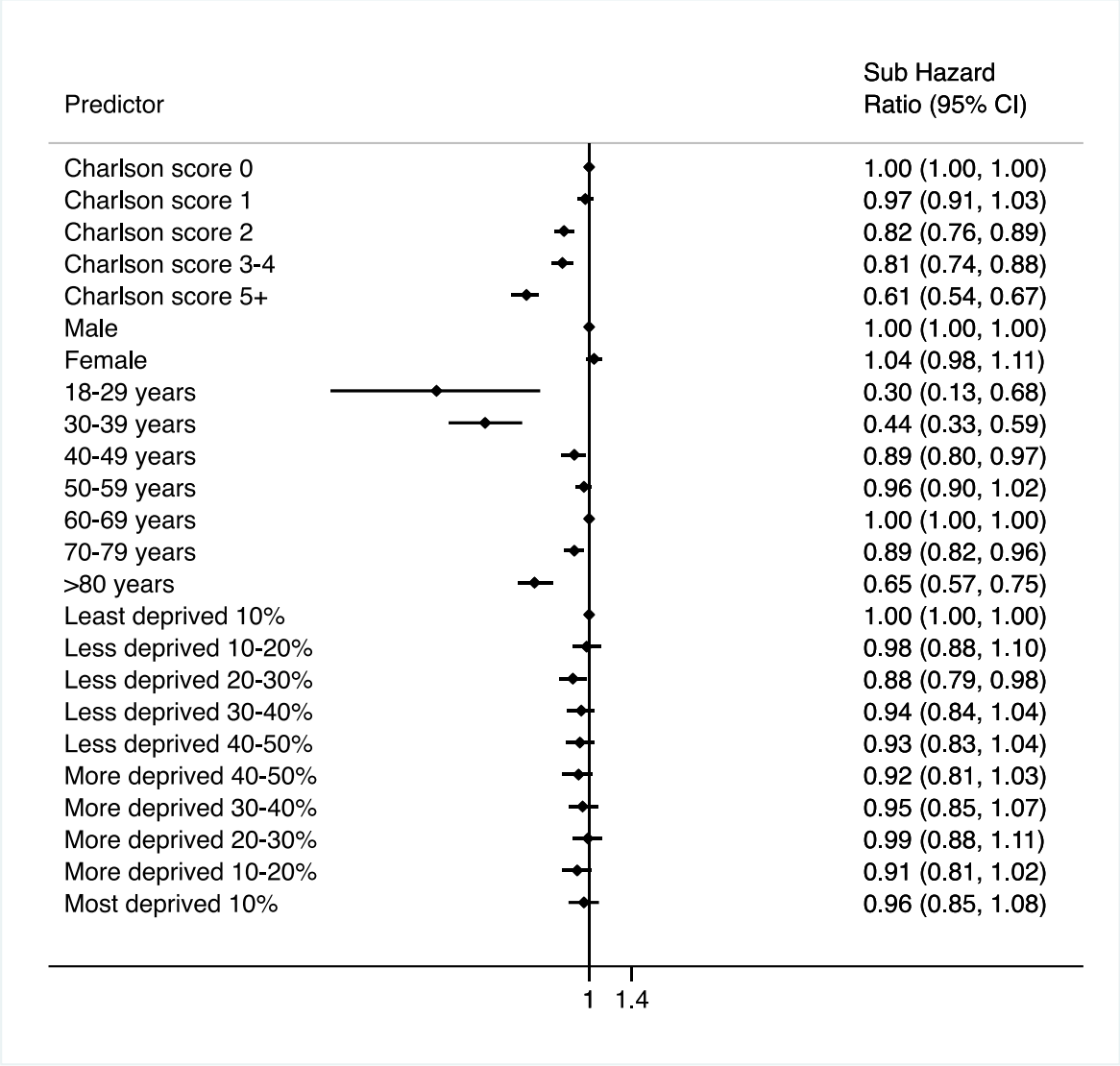


Figure 4.5 Forest plot for risk of any type of further procedure following primary BTOA injection in HES APC, NHS England 1998-2017. (see table 4.2 for absolute values)

Table 4.2 Risk of any intervention after BTOA injection using subhazard ratio (sHR) accounting for the competing risk of mortality

	Total in group	Total interventions	Crude sHR	95% CI	Adjusted sHR	95% CI
Sex						
Female	14624	7497	1.07	1.01 to 1.14	1.04	0.98 to 1.11
Age category						
18-29 years	49	7	0.32	0.14 to 0.72	0.30	0.13 to 0.68
30-39 years	280	70	0.47	0.35 to 0.63	0.44	0.33 to 0.59
40-49 years	1797	804	0.95	0.86 to 1.04	0.89	0.80 to 0.97
50-59 years	5975	3051	1.00	0.94 to 1.07	0.96	0.90 to 1.02
60-69 years	6490	3534	1 (reference)	1 (reference)	1 (reference)	1 (reference)
70-79 years	3486	1785	0.85	0.79 to 0.92	0.89	0.82 to 0.96
Over 80 years	1022	398	0.60	0.53 to 0.69	0.65	0.57 to 0.75
Charlson Comorbidity Index						
0	7881	4139	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	4486	2474	0.97	0.91 to 1.03	0.97	0.91 to 1.03
2	2535	1230	0.81	0.75 to 0.88	0.82	0.76 to 0.89
3-4	2374	1099	0.80	0.73 to 0.87	0.81	0.74 to 0.88
5+	1844	709	0.59	0.54 to 0.66	0.61	0.54 to 0.67
Index Multiple Deprivation						
Least deprived 10%	1651	911	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Less deprived 10-20	1805	987	0.98	0.88 to 1.10	0.98	0.88 to 1.10
Less deprived 20-30%	2119	1033	0.88	0.79 to 0.98	0.88	0.79 to 0.98
Less deprived 30-40%	2179	1069	0.94	0.84 to 1.05	0.94	0.84 to 1.04
Less deprived 40-50%	2030	1001	0.92	0.82 to 1.03	0.93	0.83 to 1.04
More deprived 10-20%	1760	894	0.90	0.80 to 1.01	0.92	0.81 to 1.03
More deprived 20-30%	1902	918	0.94	0.84 to 1.05	0.95	0.85 to 1.07
More deprived 30-40%	1844	932	0.98	0.87 to 1.10	0.99	0.88 to 1.11
More deprived 40-50%	1726	836	0.89	0.80 to 1.00	0.91	0.81 to 1.02

Most deprived 10%	116	43	0.92	0.82 to 1.04	0.96	0.85 to 1.08
Adjusted subhazard ratio represents results of multivariable regression analysis adjusted for all other factors included (i.e., sex, age, charlson comorbidity index and index of multiple deprivation)						

When examining the potential association of these factors with progression to surgery following primary BTOA injection, the same signals were seen (Table 4.3, Figure 4.6). A stronger effect of female sex was determined in multivariable analysis, with similar trends seen with reduced risk of intervention at the extremes of age and with increasing levels of comorbidity. No association was seen with socioeconomic status.

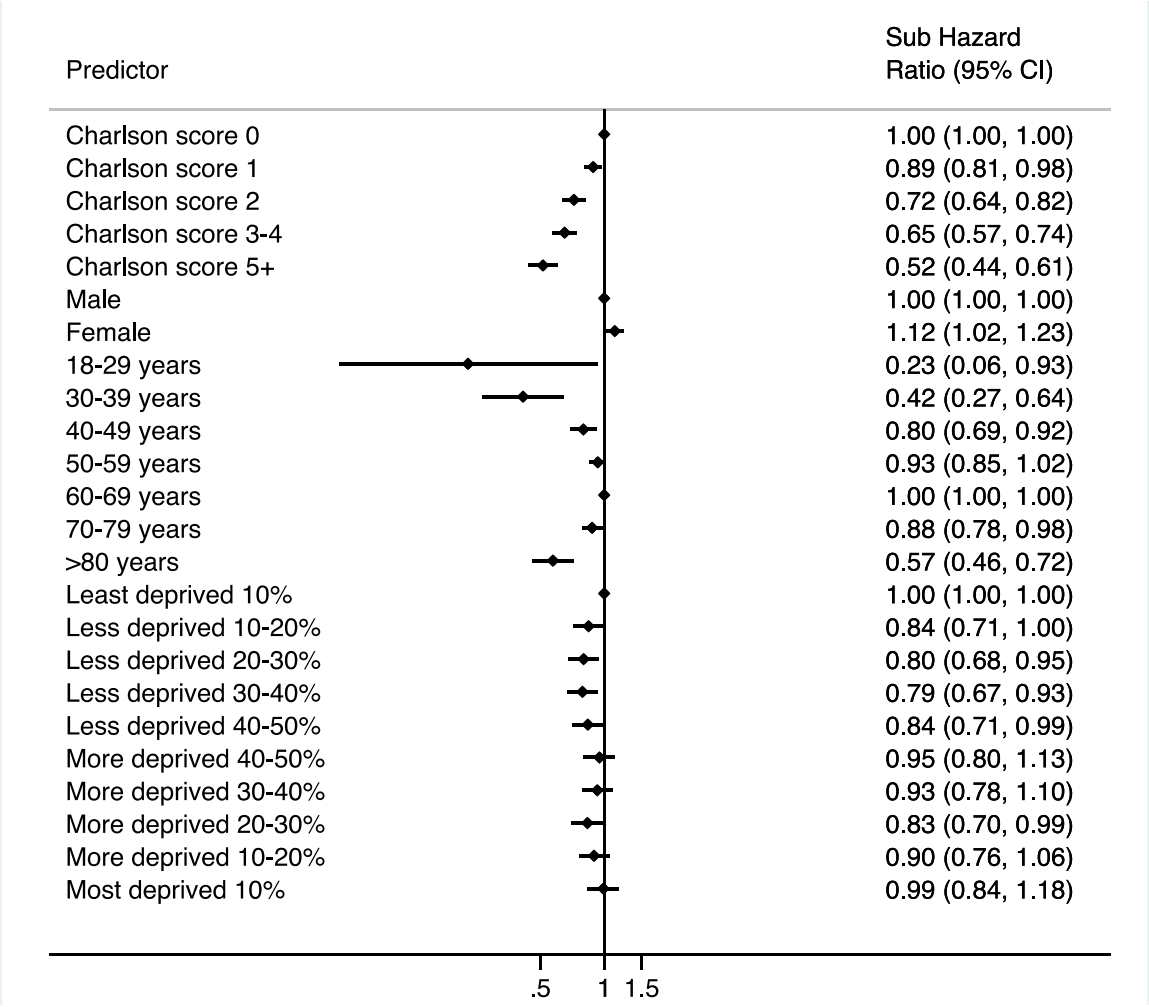


Figure 4.6 Forest for risk of surgery post primary BTOA injection in HES APC, NHS England 1998-2017. (See table 4.3 for absolute values)

Table 4.3 Risk of surgery after primary BTOA injection

	Total in group	**Total proceeding to surgery**	**Crude sHR**	**95% CI**	**Adjusted sHR**	**95% CI**
Sex						
Female	14624	3325	1.15	1.05 to 1.27	1.12	1.02 to 1.23
Age category						
18-29 years	49	<7*	0.25	0.06 to 1.00	0.23	0.06 to 0.93
30-39 years	280	23	0.47	0.30 to 0.73	0.42	0.27 to 0.64
40-49 years	1797	369	0.88	0.76 to 1.01	0.80	0.69 to 0.92
50-59 years	5975	1443	1.00	0.91 to 1.10	0.93	0.85 to 1.02
60-69 years	6490	1618	1 (reference)	1 (reference)	1 (reference)	1 (reference)
70-79 years	3486	698	0.82	0.73 to 0.91	0.88	0.78 to 0.98
>80 years	1022	123	0.51	0.41 to 0.63	0.57	0.46 to 0.72
Charlson Comorbidity Index						
0	7881	1966	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	4486	1078	0.90	0.82 to 0.98	0.89	0.81 to 0.98
2	2535	523	0.72	0.64 to 0.82	0.72	0.63 to 0.82
3-4	2374	434	0.65	0.57 to 0.74	0.65	0.57 to 0.74
5+	1844	277	0.51	0.44 to 0.60	0.52	0.84 to 1.18
Index Multiple Deprivation						
Least deprived 10%	1651	397	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Less deprived 10-20	1805	394	0.85	0.72 to 1.01	0.84	0.71 to 1.00
Less deprived 20-30%	2119	458	0.80	0.68 to 0.94	0.80	0.68 to 0.95
Less deprived 30-40%	2179	468	0.80	0.67 to 0.93	0.79	0.67 to 0.93
Less deprived 40-50%	2030	437	0.83	0.70 to 0.98	0.84	0.71 to 0.99
More deprived 10-20%	1760	394	0.92	0.77 to 1.09	0.95	0.80 to 1.13
More deprived 20-30%	1902	434	0.90	0.76 to 1.06	0.93	0.78 to 1.10

More deprived 30-40%	1844	421	0.81	0.68 to 0.97	0.83	0.70 to 0.99
More deprived 40-50%	1726	466	0.87	0.74 to 1.03	0.90	0.76 to 1.06
Most deprived 10%	116	381	0.94	0.79 to 1.11	1.00	0.84 to 1.18
Adjusted subhazard ratio represents results of multivariable regression analysis adjusted for all other factors included (i.e., sex, age, charlson comorbidity index and index of multiple deprivation) *Numbers less than 7 suppressed in line with NHS Digital disclosure control guidelines- percentages of other groups rounded to prevent secondary disclosure of data [172]						

4.4.5 Incidence of serious adverse events- BTOA injection

Overall, there were a very small number of complications identified within 30 and 90 days of primary BTOA injection. According to NHS digital rules to suppress small numbers, no precise figures for septic arthritis, wound infection (as defined by wound debridement), tendon injury requiring repair or neurovascular injury can be reported. However, all figures were below 7, generating a maximum value of 0.04% (95%CI 0.01-0.08%) for all complications within 90 days. Similarly, of the primary BTOA injections who subsequently underwent surgery (4282/19120 cases), less than 7 cases represented within the HES APC dataset with serious surgical site infection (SSI) within 90 days of surgery. This generated a maximum value of 0.16% for SSI (95% CI 0.06-0.34%) which is higher compared to the main BTOA surgery cohort below (section 4.5.5) with a rate of 0.03% for risk of serious SSI within 90 days. However, it should be recognised that a small number of cases are identified in both cohorts, and numbers were sufficiently small to prevent further analysis into the factors that could impact the incidence of post injection complications.

4.5 Results- BTOA surgery

4.5.1 Standardised incidence rates BTOA surgeries

Figure 4.7 provides the flowchart of data management for the primary BTOA surgery cohort. Over the 19-year period, HES APC recorded 43 076 primary BTOA surgeries were undertaken on 37 329 patients in the NHS in England. Most of the patients were again female and in the seventh decade (Table 4.4). Similarly low levels of comorbidity were identified in the primary BTOA surgery cohort, with the majority of patients identifying

themselves as of white ethnic background. Unlike the primary BTOA injection cohort, more patients in the primary BTOA surgery cohort were from more affluent groups in society. The majority of procedures were recorded as simple trapeziectomy, with the second most common procedure being trapeziectomy with LRTI. There was a higher incidence of men within the arthrodesis cohort who were also slightly younger, suggesting that this group may have included more patients with BTOA of post traumatic origin. There did not appear to be a difference at baseline between the socioeconomic status or overall level of comorbidities recorded for those undergoing different surgical subtypes. Further demographic granularity is given in the Appendix C Table C.6.

345 cases (0.8%) had less than 30 days of follow up without censoring (i.e., due to undergoing surgery in early 2017 at the end of the dataset), with 2.5% (1075 cases) having less than 90 days follow up. The number of patients with a short follow up period within the total cohort was not considered to be a substantial source of bias when determining rates of further intervention or post-operative serious complications.

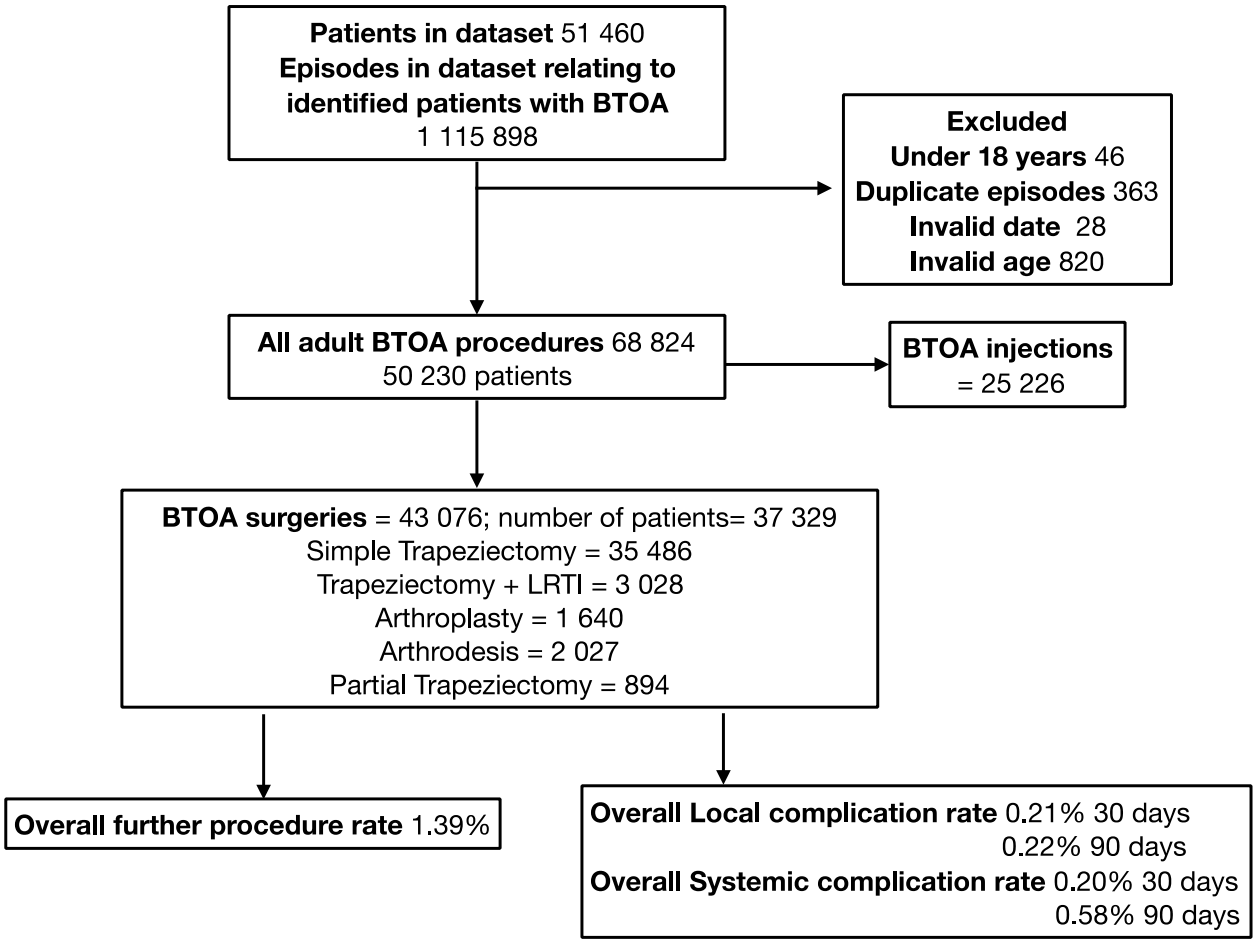


Figure 4.7 Data management flow chart, primary BTOA surgery cohort.

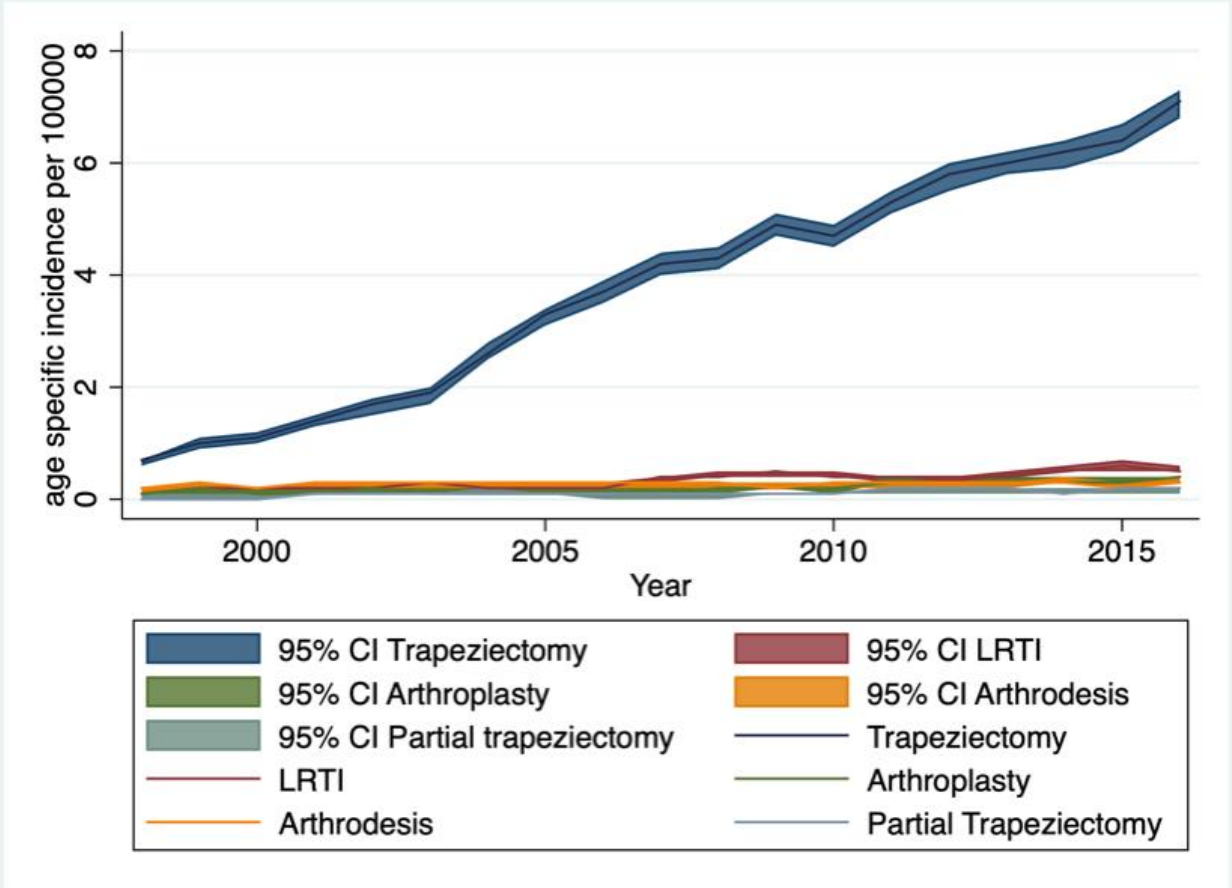
Table 4.4. Demographics of patients undergoing primary BTOA surgery

	All surgery (N, %) (total=43 076)	**Trapeziectomy N (%) (35 486)**	**LRTI N (%) (3028)**	**Arthroplasty N (%) (1640)**	**Arthrodesis N (%) (2027)**	**Partial Trapeziectomy N (%) (894)**
Female sex	34 112 (79.1)	28 655 (80.8)	2411 (79.6)	1250 (76.2)	1092 (53.9)	704 (78.7)
Mean age (SD; years)	63.2 (SD 9.2)	63.6 (SD 8.8)	62.5 (SD 9.7)	61.7 (SD 9.3)	58.1 (11.7)	63.1 (9.8)
Charlson Comorbidity index						
0	18 279 (42.4)	14 992 (42.3)	1 324 (43.8)	677 (41.3)	890 (43.9)	396 (44.3)
1	10 640 (24.7)	8 807 (24.8)	721 (23.8)	444 (27.1)	475 (23.4)	193 (21.6)
2	5 693 (13.2)	4 746 (13.4)	392 (13.0)	199 (12.1)	250 (12.3)	106 (11.8)
3	3 286 (7.6)	2 723 (7.7)	222 (7.3)	125 (7.6)	142 (7.0)	74 (8.3)
4	1 659 (3.9)	1 359 (3.8)	123 (4.1)	60 (3.7)	77 (3.8)	40 (4.5)
>=5	3 519 (8.2)	2 859 (8.0)	246 (8.1)	135 (8.2)	193 (9.6)	86 (8.5)
Index of Multiple Deprivation (IMD)						
Quintile 1 (least deprived)	9 518 (22.1)	7 949 (22.4)	582 (19.2)	435 (26.5)	348 (17.2)	204 (22.8)
Quintile 2	9 637 (22.4)	7 950 (22.4)	747 (24.6)	342 (20.9)	424 (21)	174 (19.5)
Quintile 3	7 961 (18.5)	6553 (18.5)	563 (18.6)	264 (16.1)	402 (19.8)	179 (20)
Quintile 4	8 004 (18.6)	6550 (18.5)	576 (19.1)	309 (18.8)	417 (20.6)	152 (17)
Quintile 5 (Most deprived)	7 598 (17.7)	6229 (17.5)	514 (17.0)	282 (17.2)	393 (19.4)	180 (20.1)
Missing	358 (0.8)	255 (0.7)	46 (1.5)	8 (0.5)	43 (2.0)	6 (0.7)

4.5.2 Trends in primary BTOA surgeries

An increasing trend in primary BTOA surgery undertaken was seen over the dataset. The predominant increase was in the number of simple trapeziectomies undertaken (Figure 4.8) This is in contrast to the trends seen in CTD surgeries undertaken over the 19 year period seen in chapter 3.4, which rose during the early years of the dataset and then remained static.

Figure 4.8 Trends in primary BTOA surgery, NHS England, 1998-2017



4.5.3 Incidence and trends in further procedures

The trend in further intervention following primary BTOA surgery (i.e. revision surgery or intraarticular BTOA injection) was similar to that seen following primary BTOA injection (Figure 4.9). The median follow up time was around 5 years (1835 days; IQR 816 to 3223), with the median time to further procedure being 1.5 years (472 days; IQR 272 to 965 days). Some variation in time to further intervention was seen between surgical subtypes (Table 4.5); primary arthroplasty undergoing further procedure at a median time of 732 days compared to 420 for simple trapeziectomy. The rate of further procedures during the follow up period was 1.39% (n=599/43 076, with arthroplasty (3.84%; n=63/1 640) and arthrodesis (3.50%; n=71/2027) having the highest rates of revision surgery or BTOA injection following primary intervention. Appendix C Figures C.1-C.5 details the trends in revision procedures by surgical subtype where similar trends of early further intervention are displayed.

Figure 4.9 Kaplan Meier survival plot of further procedures following primary BTOA surgery, NHS England 1998-2017

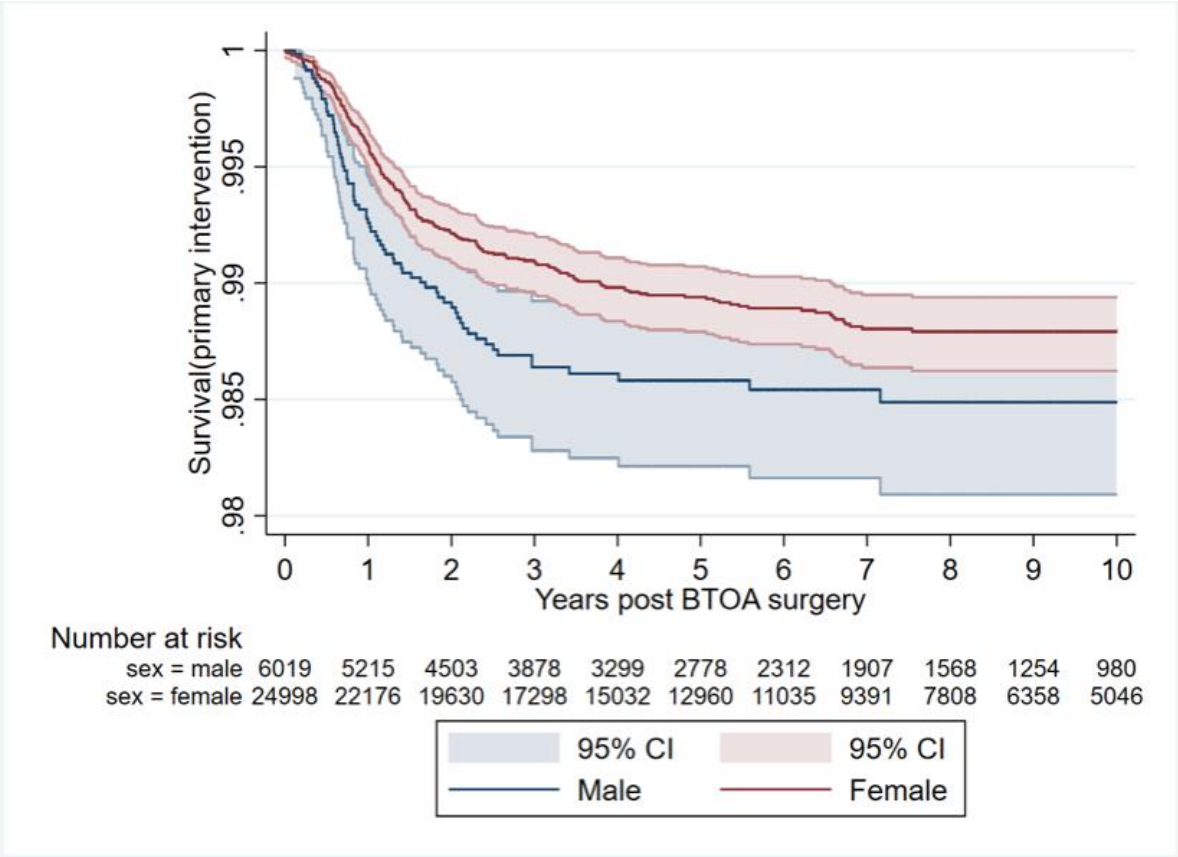


Table 4.5 Rate of further thumb base procedure (revision surgery or intraarticular steroid injection) according to BTOA surgical subtype

	Number of cases	Median follow up time in days (IQR)	Number cases needing further procedures[a] (%)	Median time to further procedure[a] in days (IQR)	Further procedure[a] rate per 1000 person years (95%CI)
All BTOA surgeries	43 076	1835 (816 to 3223)	599 (1.39%)	472 (272 to 965)	1.72 (1.54 to 1.92)
Trapeziectomy	35 486	1839 (820 to 3228)	398 (1.12%)	420.5 (248 to 804)	1.73 (1.55 to 1.93)
Trapeziectomy with LRTI	3 028	2063.5 (880 to 3405)	45 (1.49%)	508 (287 to 1648)	2.13 (1.56 to 2.92)
Arthroplasty	1 640	2000.5 (865 to 3683.5)	63 (3.84%)	732.5 (325 to 1666.5)	4.83 (3.65 to 6.40)
Arthrodesis	2 027	2712.5 (1222 to 4546)	71 (3.50%)	520 (301 to 1054)	3.91 (3.04 to 5.04)
Partial Trapeziectomy	894	1972 (929 to 4070)	22 (2.46%)	673.5 (296.5 to 1599.5)	2.63 (1.59 to 4.37)

[a] Further thumb base procedure only (intra-articular steroid injection or revision surgery)

4.5.4 Factors affecting the incidence of further procedures

Due to the low numbers of further procedures undertaken in the younger age groups, a decision was made *a priori* to only undertake multivariable regression analysis in those aged over 40 years. Men, and those aged 40-49 had an elevated risk of further procedures that was maintained within the multivariable analysis adjusted for age, sex, CCI and IMD whilst taking into account the competing risk of mortality (Table 4.6). Those from lower socioeconomic groups also had an increased risk of further procedure despite adjustment for these factors, although this did not follow an obvious stepwise trend throughout all deciles.

When adding the surgical subtype undertaken as an exposure variable, age no longer appeared associated with further procedure within the multivariable model (Table 4.7). Male sex remained associated with an increased risk of revision surgery or post-operative BTOA injection, but more striking was the association with surgical subtype. Those undergoing arthrodesis or arthroplasty had over 2.4 times the risk of further procedure compared to those undergoing simple trapeziectomy (number of further procedures following trapeziectomy= 398/35 486 compared to arthroplasty n=63/1640 or arthrodesis n=71/2027). This may suggest that the reason men and those with disease at a younger age were more likely to undergo further intervention may be due to primary surgical subtype rather than their demographics themselves, or an unknown confounding factor associated with the surgical choice of procedure. The forest plot in Figure 4.10 illustrates the relative influence of each factor within the multivariable analysis adjusted for all included factors.

Table 4.6 Risk of further procedure (revision BTOA surgery or BTOA injection), all primary BTOA surgeries

	Total in group	**Total further procedures**	**Crude sHR[a]**	**95% CI**	**Adj sHR[a]**	**95% CI**
Male	8964	138	1.22	0.99 to 1.49	1.24	1.01 to 1.52
Age						
40-49 years	2 595	52	1.53	1.11 to 2.12	1.53	1.10 to 2.13
50-59 years	12 930	197	1.12	0.91 to 1.38	1.14	0.92 to 1.40
60-69 years	17 227	233	1 (ref)	1 (ref)	1 (ref)	1 (ref)
70-79 years	8 531	102	0.86	0.66 to 1.10	0.85	0.66 to 1.10
>80 years	1 397	13	0.66	0.36 to 1.21	0.66	0.36 to 1.22
Charlson comorbidity index						
0	18 279	237	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	10 640	158	1.14	0.92 to 1.42	1.17	0.94 to 1.46
2	5 693	78	0.99	0.75 to 1.31	1.06	0.80 to 1.40
3+	8 464	126	0.92	0.73 to 1.17	1.01	0.78 to 1.30
IMD						
Least deprived 10%	4 749	55	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Less deprived 10-20%	4 769	52	1.03	0.69 to 1.54	1.03	0.68 to 1.54
Less deprived 20-30%	4 819	67	1.16	0.78 to 1.72	1.14	0.77 to 1.70
Less deprived 30-40%	4 818	57	1.08	0.73 to 1.61	1.07	0.72 to 1.60
Less deprived 40-50%	4 682	74	1.24	0.84 to 1.83	1.21	0.82 to 1.79
More deprived 40-50%	3 279	49	1.04	0.66 to 1.62	0.99	0.63 to 1.55
More deprived 30-40%	3 798	52	1.24	0.82 to 1.86	1.18	0.79 to 1.78
More deprived 20-30%	4 206	75	1.66	1.14 to 2.42	1.61	1.10 to 2.34
More deprived 10-20%	4 559	76	1.51	1.04 to 2.20	1.47	1.01 to 2.15
Most deprived 10%	3 039	38	1.03	0.65 to 1.63	0.98	0.62 to 1.55

[a] Subhazard ratio
IMD = index of multiple deprivation

Table 4.7 Risk of further procedure (revision BTOA surgery or BTOA injection), all primary BTOA surgeries, surgical subtype

	Total in group	**Total further procedures**	**Crude sHR[a]**	**95% CI**	**Adj sHR[a]**	**95% CI**
Male	8964	138	1.22	0.99 to 1.49	1.11	0.89 to 1.38
Age						
40-49 years	2 595	52	1.53	1.11 to 2.12	1.24	0.95 to 1.87
50-59 years	12 930	197	1.12	0.91 to 1.38	1.09	0.88 to 1.34
60-69 years	17 227	233	1 (ref)	1 (ref)	1 (ref)	1 (ref)
70-79 years	8 531	102	0.86	0.66 to 1.10	0.86	0.67 to 1.11
>80 years	1 397	13	0.66	0.36 to 1.21	0.67	0.37 to 1.24
Charlson comorbidity index						
0	18 279	237	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	10 640	158	1.14	0.92 to 1.42	1.17	0.94 to 1.46
2	5 693	78	0.99	0.75 to 1.31	1.05	0.79 to 1.40
3+	8 464	126	0.92	0.73 to 1.17	0.99	0.77 to 1.28
IMD						
Least deprived 10%	4 749	55	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Less deprived 10-20%	4 769	52	1.03	0.69 to 1.54	1.00	0.67 to 1.50
Less deprived 20-30%	4 819	67	1.16	0.78 to 1.72	1.13	0.76 to 1.67
Less deprived 30-40%	4 818	57	1.08	0.73 to 1.61	1.06	0.71 to 1.58
Less deprived 40-50%	4 682	74	1.24	0.84 to 1.83	1.19	0.81 to 1.77
More deprived 40-50%	3 279	49	1.04	0.66 to 1.62	0.98	0.63 to 1.53
More deprived 30-40%	3 798	52	1.24	0.82 to 1.86	1.16	0.77 to 1.75
More deprived 20-30%	4 206	75	1.66	1.14 to 2.42	1.58	1.09 to 2.29
More deprived 10-20%	4 559	76	1.51	1.04 to 2.20	1.45	1.00 to 2.11
Most deprived 10%	3 039	38	1.03	0.65 to 1.63	0.96	0.61 to 1.52

Surgery subtype						
Simple trapeziectomy	35 486	398	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Trapeziectomy + LRTI	3 028	45	1.22	0.86 to 1.73	1.16	0.82 to 1.66
Arthroplasty	1 640	63	2.51	1.81 to 3.48	2.49	1.80 to 3.44
Arthrodesis	2 027	71	2.55	1.91 to 3.40	2.40	1.78 to 3.26
Partial Trapeziectomy	894	22	1.44	0.81 to 2.55	1.46	0.82 to 2.59
[a] Subhazard ratio IMD = index of multiple deprivation						

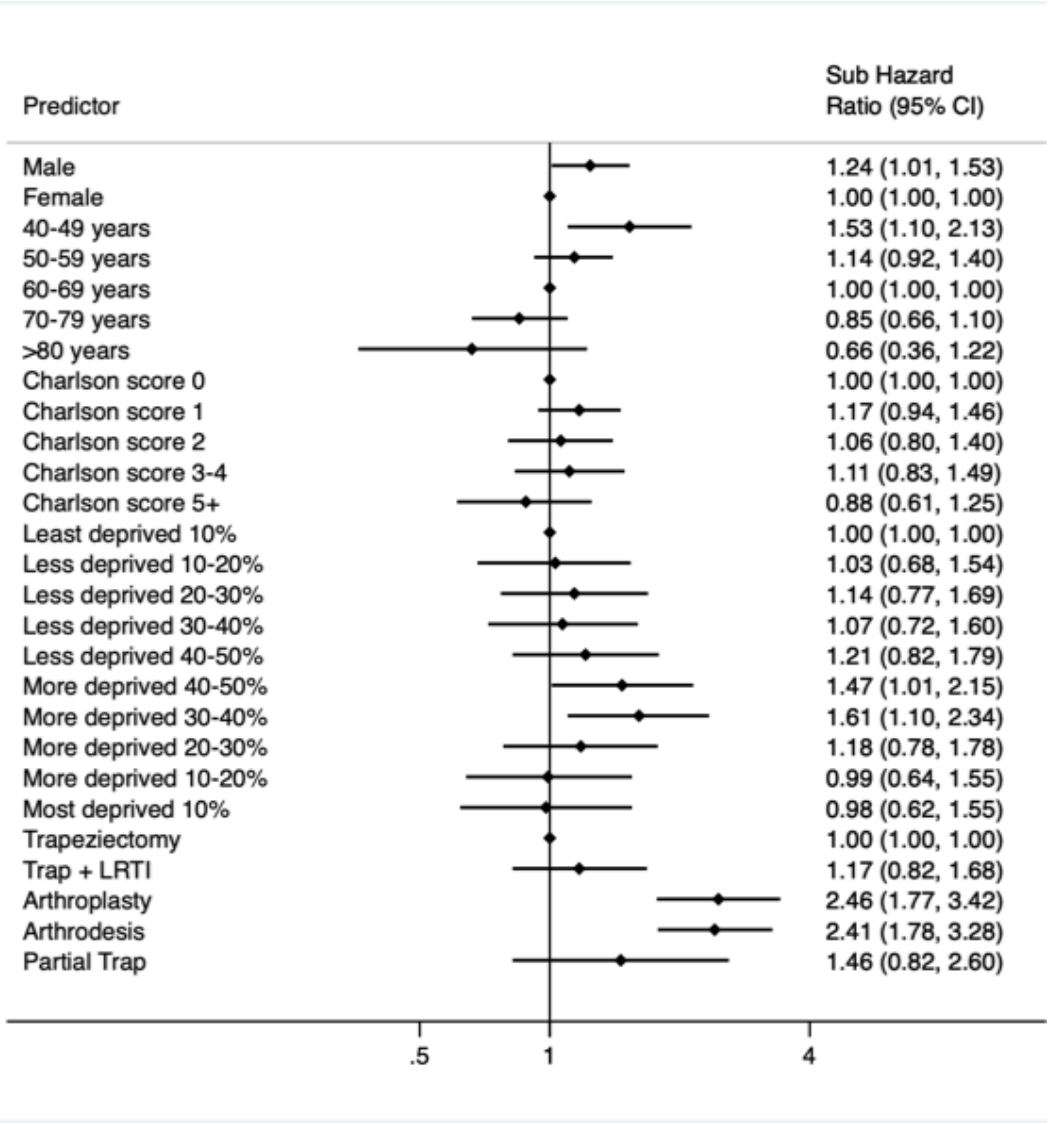


Figure 4.10 Forest plot, incidence of further intervention following primary BTOA surgery, adjusted subhazard ratio. (See table 4.7 for absolute values)

Tables C.7-C.10 in Appendix C illustrate the individual multivariable models run for the risk of further procedure divided by surgical subtype. As was seen in the main analysis, the risk of further procedure following trapeziectomy was increased for men, but age, CCI and IMD was not associated. For LRTI, younger age appears to be associated with increased risk of further procedure, but no other factor, and no factors appeared to be associated within the arthroplasty and arthrodesis models. It should be noted that the vast majority of the cohort

underwent simple trapeziectomy, and therefore these groups may be underpowered in this sensitivity analyses.

4.5.5 Incidence of serious adverse events- BTOA surgery

Similarly to CTD in Chapter 3, there was a low rate of post-operative complications found. The risk of local complications was 0.22% (n=93/43 076) within 90 days of surgery, with the risk of a systemic complication at 0.58% (n= 250/ 43 076, Tables 4.6; Table C.11 in Appendix C gives further detail by surgical subtype). No further analysis of the factors associated with complications was undertaken due to the low rate of complications.

Table 4.6. Local complications and systemic events following all BTOA surgery

	Time	All surgery N (%[95%CI])
Local complications		
Wound dehiscence and wound infection	Within 30 days	12 (0.03% [0.01-0.05])
	Within 90 days	14 (0.03% [0.02-0.05])
Neurovascular injury	Within 30 days	79 (0.18% [0.15-0.23])
Any complication	Within 30 days	91 (0.21% [0.17-0.26]
	Within 90 days	93 (0.22% [0.17-0.26]
Systemic events		
Stroke	Within 30 days	9 (0.02% [0.01-0.04])
	Within 90 days	40 (0.09% [0.07-0.13])
Respiratory Tract infection	Within 30 days	70 (0.16% [0.13-0.21])
	Within 90 days	174 (0.40% [0.35-0.47])
Myocardial infarction	Within 30 days	17 (0.04% [0.02-0.06])
	Within 90 days	50 (0.11% [0.09-0.15])
DVT/PE	Within 30 days	18 (0.04% [0.02-0.07])
	Within 90 days	41(0.10% [0.07-0.13])
UTI	Within 30 days	30 (0.07% [0.05-0.10]
	Within 90 days	75 (0.17% [0.14-0.22])
Acute Renal Failure	Within 30 days	13 (0.03% [0.02-0.05])
	Within 90 days	44 (0.10% [0.07-0.14])
Any Systemic Event	Within 30 days	87 (0.20% [0.16-0.25])
	Within 90 days	250 (0.58% [0.51-0.66])
Any Systemic Event (excl UTI & ARF)	Within 30 days	44 (0.10% [0.07-0.14])
	Within 90 days	131 (0.30% [0.25-0.36])

4.6 Discussion

4.6.1 Key findings

This study of interventions for BTOA in a nationalised health care system has shown that only half of patients undergoing BTOA injection in secondary care proceed to further intervention. Less than one in four registered as undergoing BTOA injection went onto subsequent surgery, both surgery and repeat injection mostly occurring within 18 months of primary injection. When investigating factors that were associated with any further intervention, those at extremes of age or with a higher charlson comorbidity index were less likely to undergo any intervention, although female sex was associated with an increased risk of progressing to surgery. A very low overall rate of serious adverse events was seen following injection, with 4 in 10,000 primary injections being complicated by a hospital admission for infection, neurovascular or tendon injury. Those who went on to subsequent surgery had a higher rate of complications than those who had not undergone a preoperative injection, but the overall rates were still low with serious infection being less than 2 in 1000 within the first 90 post-operative days.

For primary BTOA surgery, this study found an increasing trend in the amount of surgery being undertaken over the last 19 years, with the predominant increase in simple trapeziectomy. Overall reintervention rate was 1.39% (n=599/ 43 076), with reintervention occurring within the first 18 post-operative months as seen with BTOA injection. Whilst overall reintervention rates were low, those undergoing arthroplasty or arthrodesis were around 2.5 times more likely to proceed to a second intervention when compared to simple trapeziectomy (number of further procedures following trapeziectomy= 398/35 486

compared to arthroplasty n=63/1640 or arthrodesis n=71/2027). This suggests that further epidemiological studies in this area should be undertaken as occurs with arthroplasties at other anatomical sites.[176, 177]

Methodologically, whilst further validation work was needed surgical subtypes were able to be identified. Reoperation was also found where laterality identified. Similarly to chapter 3, the low rate of complications may be related to the requirement for hospital admission. The increasing trend in injections recorded in the HES APC dataset may reflect a change in coding practice rather than a significant increase. The small number of LRTI may reflect the high reliance on coding practice, and the validation study undertaken in OUH may not be representative nationally.

4.6.2 Strengths and Limitations

As discussed in chapter 3, a great strength of this study is the ability to include the national workload of interventions through identifying all work that has been remunerated by the NHS. The ability to identify an individual patient who moves within a nationalised healthcare system enables further interventions outside of the initial provider to be identified, including those that move geographically around the country, or seek second opinion elsewhere. This enables better identification of rates of reintervention than is possible in other single centre cohorts, administrative or claims datasets that do not have universal data capture as is possible within HES APC. A nationalised healthcare system that covers the vast proportion of health care provided in England also ensures that the cohort includes those at the extremes of age with a wide sociodemographic mix of backgrounds. This

enables results to be more aligned to routine clinical practice, and potentially more generalisable than those produced within clinical trials. The ability to undertake longitudinal follow up over a prolonged period of time is also a benefit over clinical trials and one of the areas in which routinely collected data has an advantage.

Other areas of musculoskeletal research have already used HES APC to investigate the safety of surgery, utilising the ability to have longer term follow up.[173, 175] For BTOA surgery, this study enables comparison of surgical subtypes within routine clinical practice that is difficult in other clinical studies due to the heterogeneity of surgeries undertaken and lack of statistical power.[106, 112] This large cohort in addition to the longitudinal follow up enables this study to add to the literature, especially when considering the likelihood of subsequent intervention after primary surgery. The current literature had suggested that early age may be associated with increased risk of revision, but this large-scale multivariable analysis suggests that it may in fact be surgical subtypes undertaken more frequently in young patients that are the cause for increased rates of revision surgeries. [119, 120]

Whilst HES APC will identify interventions in the NHS, it will not capture those who undertake interventions in the private sector or identify those who leave the UK and subsequently sustain a complication or further procedure. Private healthcare remains a small proportion of the market in the UK, and whilst any NHS activity undertaken in private providers will be captured it must be acknowledged that private healthcare practice will not be contained in this study.[130] Similarly, whilst emigration is low, anyone who subsequently left the UK will appear to have required no further intervention inaccurately.[166] Finally,

being an administrative dataset enables the data captured within to suffer a reduced risk of inclusion bias at the hands of a research team.

The main limitation of this work is that it is restricted to secondary care only, and only interventions that are registered as requiring hospital admission. This is particularly important for BTOA injection, where traditionally the majority of these were undertaken in outpatient clinic or primary care. Those injections will not be captured in HES APC, and therefore injections registered in the dataset may represent a selective subgroup of patients. In order to minimise this bias, I led validation studies in order to determine what HES APC contained and concluded that it was injections undertaken under radiological guidance, in theatre, or in specialist clinicals. The study's results can therefore only be interpreted in relation to those undergoing BTOA injection in secondary care in one of these treatment pathways. As prior injections in outpatient clinic or primary care cannot be identified, it may also be true that 'primary' BTOA injection is only the primary injection in secondary care.

The selection bias of what is recorded in HES APC extends also to the identification of complications. This dataset will only identify complications that require at least a day case admission in secondary care, and therefore will only identify the most serious adverse events. The past medical history generated from prior episodes of care is also only generated from admissions within secondary care, so any conditions treated in primary care will not be identified. Whilst I have attempted to minimise the risk of misclassification of both cases and serious adverse events through the use of validation studies, there remains the risk that data generated in an administrative dataset may not truly represent the

condition. Every effort has been taken to remove patients who have a code relating to a traumatic event in the same episode as surgery in addition to codes specifically relating to post traumatic OA, but there is a still a risk that confounding by indication may occur between surgical subtypes. Patients who present with increased instability with post traumatic OA for example may be more likely to proceed to arthrodesis, and without further information surrounding the surgical decision-making process it is difficult to determine why a certain surgical procedure was chosen.

4.6.3 Comparison to other studies

This study generates new evidence for the role of both BTOA injections and BTOA surgery in routine clinical practice. Prior studies from the US in both Medicare (state assisted) and insurance-based healthcare had suggested high rates of surgical complications in patients who underwent prior BTOA injection.[89] No absolute rates of complications were able to be determined due to the nature of the claims dataset used but concerns about an increased odds of up to 20% for post-surgical complications were raised. Here, I identified an increased rate of complications for those undergoing pre-operative injection, but the rate of complications remained less than 2 in 1000, and therefore the absolute risk of complication remains very low suggesting that pre-operative BTOA injection is safer than previously thought.

This study concurs with current literature that suggests higher rates of revision surgery are seen with arthroplasty compared to techniques such as simple trapeziectomy.[112] This systematic review was based in smaller clinical studies, and therefore these new results

emphasise that higher rates of reoperation are also seen within a large national cohort in routine clinical practice. Whilst rates are higher with arthroplasty and arthrodesis, this study provides evidence that there is an overall low rate of reoperation and serious complications and that demographic factors do not appear to be significant in driving the association with adverse outcome.

4.6.4 Future research

As discussed in Chapter 3, the disadvantage of HES APC being based in admitted patient care highlights the need for work to identify minor complications and adverse outcomes that would not be registered in this dataset. This could be undertaken in primary or intermediate care in order to determine complications such as wound infection requiring only antibiotics, or persistent scar tenderness or complex regional pain syndrome presenting to specialist outpatient services. Study in primary, intermediate or outpatient settings would also enable a greater understanding of patient comorbidity outside those conditions registered within HES APC. This will identify those with comorbidities that are less severe and would give greater levels of information regarding the potential risk of poor outcome associated with other medical conditions.

This study into the safety of BTOA injections cannot identify complications such as a flare response to steroids or skin depigmentation, and therefore future work could aim to identify these conditions in other large scale routinely collected data sources. Similarly, this work only focusses upon intra-articular injections, that in the NHS would identify steroid injection rather than injection of other substances such as hyaluronic acid or fat not

routinely undertaken in the English public healthcare system. Future work is needed to compare these substances within routine clinical care.[81-84]

This work identified that female sex was associated with progression to surgery following primary BTOA injection, and further work is needed to identify the reason for this gender difference. For the surgical analysis, the multivariable regression model to identify risk factors for adverse events only focussed upon patient factors and does not attempt to identify if the variation was associated with surgeon, surgery, or hospital based healthcare factors. Multilevel regression modelling techniques in future work could help to untangle the complicated interaction of these factors in determining outcome from surgery. As this work also identified an increased risk of further procedure with arthroplasty, future work could focus upon identifying the types of BTOA arthroplasties used in clinical practice. Unfortunately HES APC only uses a generic code for BTOA arthroplasties, and therefore this dataset cannot identify if a certain implant is driving the increased rate of revision surgery. Focus upon implant registries as have been used in hip and knee arthroplasty could improve our understanding of the cause of implant failure in the treatment of BTOA.[20, 21]

Overall, this study focusses upon 'successful' outcome from surgery being that of a lack of revision surgery or complication and focusses upon safety as a proxy for outcome. The following chapter will focus upon the true patient perspective of outcome from intervention using patient reported outcome measures, and further work to undertake this in those undergoing primary BTOA injection would be worthwhile to better understand the role of this procedure in the treatment of BTOA in routine clinical practice.

5. UK Hand Registry

Patient Reported Outcomes after surgery for Base of Thumb Osteoarthritis- UK Hand Registry[‡]

Contributions: All work in this chapter was designed, conducted and analysed by myself apart from section 5.4.3 Mixed effect regression analysis, where R code development, and the generation of plots 5.4 and 5.4 were undertaken with assistance from Dr Edward Burn. Senior advice was gratefully received from Mr Matthew Gardiner and Prof Jeremy Rodrigues.

5.1 Summary

Debate surrounds the benefits of simple trapeziectomy and trapeziectomy with ligament reconstruction and tendon interposition (LRTI) for treating base of thumb osteoarthritis (BTOA). This study of the UK Hand Registry (UKHR) evaluates the impact of the two techniques upon voluntarily collected patient-reported outcomes (PROMs). Data was collected over a six year period, and PROMs at baseline and three, six and 12 months postoperatively were compared. A mixed effects regression model was used to capture the change in trajectory of PROMs post operatively. Overall there was an improvement in general and hand specific quality of life measures, without a clinically meaningful difference

[‡] [‡] Parts of this content have been published in Journal of Hand Surgery (Europe).178. Lane JCE, Rodrigues JN, Furniss D, Burn E, Poulter R, Gardiner MD. Basal thumb osteoarthritis surgery improves health state utility irrespective of technique: a study of UK Hand Registry data. The Journal of hand surgery, European volume. 2020;45(5):436-42.

between those treated with trapeziectomy or trapeziectomy with LRTI (LRTI). Therefore, this work supports the role of surgery in improving symptoms for BTOA but finds no added benefit of LRTI over simple trapeziectomy.

5.2 Introduction

Despite being described in the literature for over 70 years, there is no consensus agreement upon which surgical procedure for BTOA gives the best outcome to patients.[107, 108] Whilst RCTs have focussed upon trapeziectomy and trapeziectomy with some form of ligament reconstruction, the majority of evidence supporting advanced techniques beyond these has been derived from lower level studies.[90, 93, 94, 96-98, 179] Owing to this lack of consensus opinion in the literature, a variety of techniques continue to be used. Epidemiological work has shown that the use of more complex techniques such as trapeziectomy plus ligament reconstruction and tendon interposition (LRTI), arthroplasty, arthrodesis, and osteotomy remain widespread globally, especially in the United States.[92, 93, 109, 110] There has been little work focussed upon the role of surgery for BTOA in routine clinical practice, and especially studying the patient reported outcome following surgery. Many studies instead focus on the proxies for outcome of revision surgery and complication rates, that remain surgeon focussed. There have been small studies that have compared PROMS for BTOA surgery, but these have neither compared surgical techniques for BTOA surgery or looked at a national dataset. [121-124] By comparison, other areas of orthopaedic surgery are now well adapted to using routinely collected data to assess the impact of surgery upon quality of life using PROMS.[19, 22, 180, 181]

Collection of routine data associated with surgical practice is in its infancy in UK hand surgery. This study aimed to use the UKHR for the first time to develop a greater understanding of the impact of BTOA surgery upon patient reported outcome measures taken from routine UK surgical practice. The second aim was to compare the change in PROMS between surgical subtypes where possible to determine if one technique should be favoured over another.

The methodological aim of the chapter was to interrogate the UK Hand registry to determine its value in research into patient reported outcomes following surgery, with a view to developing a better understanding of the value of disease specific prospective registries, especially those that stand alone from administrative data sources.

5.3 Methods

This study included all consecutive adult patients entered into the UKHR at the time of undergoing elective BTOA surgery between 01/02/2012 and 31/01/2018. Greater detail regarding the scope and role of the UKHR is given in Chapter 2.5. Inclusion in the UKHR is voluntary, with patients recruited by their operating surgeon who then enters details of the surgery undertaken. Patients are subsequently contacted independently from their surgeon to complete both pre- and post-operative PROMS. Age, sex, and geographical location in addition to surgical subtype as recorded by the surgeon was collected.

5.3.1 Outcomes

Two outcome measures were used to identify the impact of surgery upon patient quality of life. Firstly, EQ5D index was used to measure the impact of surgery on overall quality of life,

and to enable comparison to other healthcare interventions.[182, 183] EQ5D index can have negative values, indicating a state worse than death, with a range -0.8 (worst state) to 1 (best state imaginable). For hand function, a UK designed, hand focussed PROM called Patient Evaluation Measure (PEM) was used. This analysis focussed on section 2 of the PEM, which specifically evaluates hand function, and used the original 10 question version.[137, 139, 184] PEM part 2 has been used to evaluate a variety of hand conditions, but there is no validated minimally clinically important difference (MCID) defined in the literature for BTOA, although it has been suggested to be 2.8-3 for patients with Dupuytren's disease, another hand specific condition treated with elective surgery.[185] EQ5D and PEM part 2 were collected at baseline, and at 3, 6 and 12 months following surgery.

5.3.2 Statistical Analysis

Total scores and item-level scores were generated for all patients. PEM part 2 generated a score ranging from 10-70, and EQ5D index was generated using Euroqol crosswalk for the utility index for UK patients, giving a range from -0.594 to 1.0.[138]

Two analyses were undertaken. Firstly, the change between the baseline score and each follow up point was generated (termed the 'delta' score) to note the change in score post operatively. The value for each individual was calculated, and then the median value for the cohort calculated. Kruskal Wallis and Mann Whitney U tests were undertaken after interrogation of the data identified a non-parametric distribution of scores.

Secondly, the trajectory of change in PROM scores over the post-operative period was analysed using mixed effects regression modelling. This model was used to determine the

impact of surgical subtype, sex, age and both baseline EQ5D and PEM part 2 scores upon outcome and can take multiple post-operative scores into account for an individual. Patients were included in this analysis if they had a minimum of a pair of baseline and post-operative PROM measurement at any timepoint. Again, no imputation was undertaken, but the model estimated the values of missing datapoints, based upon it being missing at random. PROM scores were considered as continuous variables. In initial exploration, PEM part 2 was considered to have a linear relationship with age, sex and baseline PROM values, but there appeared to be non-linearity displayed between age and baseline EQ5D index with post-operative EQ5D index. This best fit a cubic splines function and this was therefore used for EQ5D index analysis.

5.4 Results

Overall, the majority of patients added to the UKHR underwent either simple trapeziectomy or trapeziectomy with LRTI (Table 5.1). Due to the low numbers of patients undergoing other procedures, further analysis was only possible with comparison between trapeziectomy or trapeziectomy plus LRTI. In the trapeziectomy and LRTI groups, baseline demographics, and baseline PROMs appeared to be comparable (Table 5.2). Whilst there were fewer surgeries added in the first year of the UKHR, potentially due to increasing adoption of the registry in practice, the spread of procedures across time otherwise did not appear to be a source of potential bias.

Table 5.1 Procedure subtypes included in UKHR

Procedure	**Frequency**	**Percent**
Trapeziectomy	749	51.4
Trapeziectomy with LRTI	648	44.5
Total/Hemi arthroplasty	25	1.7
'Revision'	16	1.1
Prosthetic spacer	7	0.5
CMC fusion	7	0.5
Prosthetic ligament stabilization	2	0.14
1st MC extension osteotomy	1	0.07
CMC stabilization	1	0.07
	1456	100

Table 5.2 Baseline characteristics for patients undergoing trapeziectomy versus LRTI

	Full dataset (Trapeziectomy)	**Full dataset (Trapeziectomy with LRTI)**	**Included in Regression analysis**
Number of patients included	749	648	746
Median Age (IQR)	67 (60 to 72)	66 (59 to 71)	67.0 (60.0 to 72.0)
Female Sex (%)	77.1	78.1	78.8
Median Baseline PEM part 2 score (IQR)	49 (41 to 56)	49 (40 to 55)	50.0 (42.0 to 56.0)
Median baseline EQ5D index (IQR)	0.69 (0.26 to 0.80)	0.66 (0.26 to 0.78)	0.6 (0.2 to 0.8)

Figure 5.1 shows the collection of PROMS from the trapeziectomy and LRTI groups post operatively, and the significant reduction in the number of completed PROMs returned post operatively. To assess for risk of inclusion bias for those with and without completed post-

operative PROMs, the baseline demographics of those with and without completed follow up PROMs Appendix D Table D.1. No difference was seen within the limited information available.

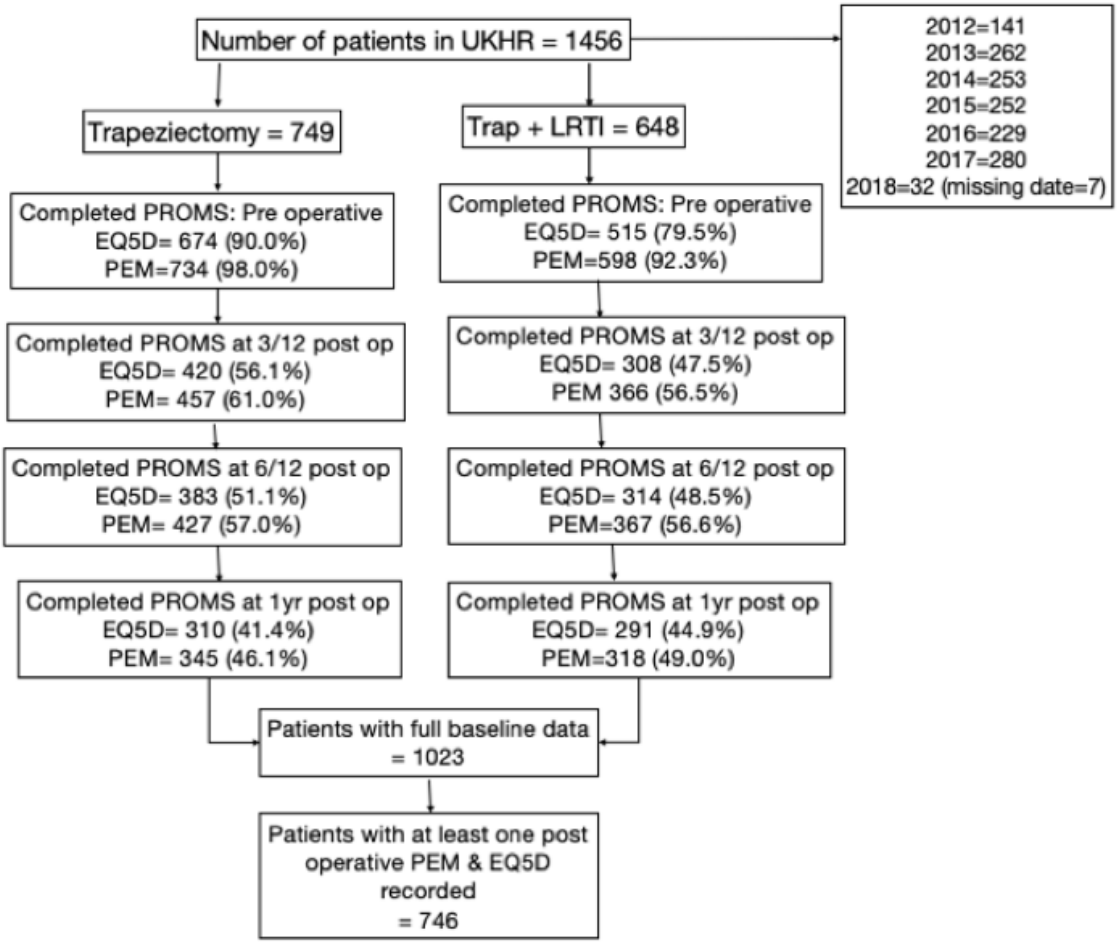


Figure 5.1 Available completed PROMs, trapeziectomy and LRTI subgroups

5.4.1 General Quality of Life- EQ5D index

Overall, an improvement was seen in EQ5D index post operatively in the cohort (median change +0.07 (IQR -0.02 to 0.25) at 3 months +0.10 (0 to 0.29) at 6 months, n=664; +0.15 (0 to 0.4) at 12 months post operatively (Table 5.3) No significant difference was seen in scores for those who underwent trapeziectomy versus LRTI at 3 or 12 months (p =0.20 and 0.57 respectively), with a 0.05 difference seen at 6 months (p=0.04). This difference in EQ5D represents a non-clinically meaningful difference between the two surgical cohorts (Figure 5.2)

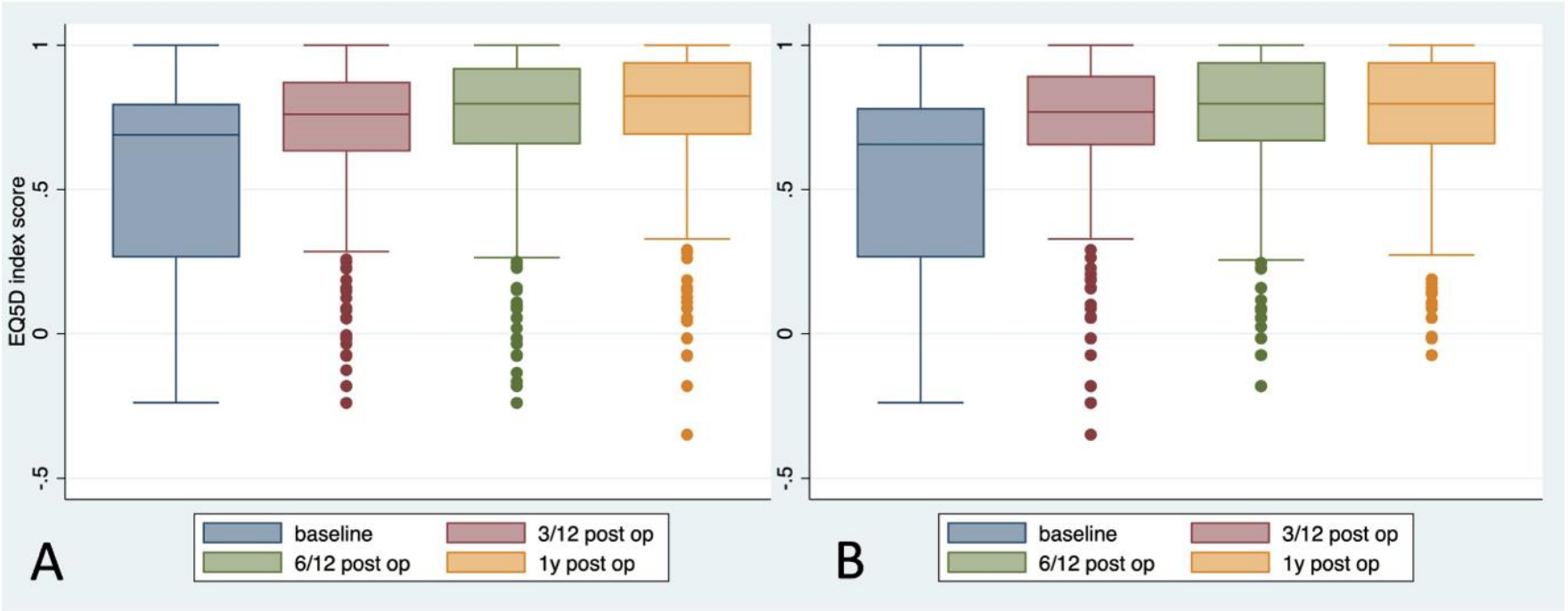


Figure 5.2. Box and whisker plot of the EQ5D index score following A) trapeziectomy, and B) trapeziectomy + LRTI
where the box represents the interquartile range, the line within the box is the median, and the whiskers represent 1.5 times the IQR above the 75th percentile, and 1.5 times the IQR below the 25th percentile.

Table 5.3 Median change in PROMS post-operatively

	EQ5D index			PEM part 2		
	3 months median score change (IQR)	**6 months median score change (IQR)**	**1 year median score change (IQR)**	**3 months median score change (IQR)**	**6 months median score change (IQR)**	**1 year median score change (IQR)**
All patients	0.07 (-0.02 to 0.25)	0.10 (0 to 0.29)	0.15 (0 to 0.40)	-18 (-29 to -6)	-22 (-31 to -10)	-22 (-33 to -10)
Trapeziectomy	0.07 (-0.04 to 0.24)	0.08 (-0.04 to 0.24)	0.16 (0.004 to 0.42)	-18 (-29 to -6)	-21 (-31 to -9)	-22 (-33 to -10)
Trapeziectomy with LRTI	0.06 (0 to 0.28)	0.13 (0 to 0.34)	0.14 (0 to 0.37)	-18 (-29 to -7)	-23 (-31 to -10)	-23 (-32 to -10)

5.4.2 Hand Specific function: PEM Part 2

A similar overall improvement in PEM Part 2 scores were also seen after surgery with a median change -18 (IQR -29 to 6) at 3 months; -22 (-31 to -10) at 6 months, -22 (-33 to -10) at one year post-operatively (Table 5.3). No difference was seen between those undergoing trapeziectomy or LRTI at any post-operative time point (Figure 5.3).

5.4.3 Mixed effect regression analysis

Only 749 patients in total had paired completed baseline and postoperative PROMs on at least one of the follow up time points, although these patients had similar baseline values to the whole cohort. (Table 5.2). Figures 5.4 and 5.5 show the change in scores over the post-operative time period for both PEM part 2 and EQ5D. There appeared to be no statistical interaction between time after surgery and post-operative PEM part 2 or EQ5D index either within the mixed effects regression model. No clinically meaningful difference was seen between the surgical subtypes, despite LRTI showing a slightly reduced improvement in PEM part 2 score compared to trapeziectomy (Table 5.4; regression coefficient -0.4). The greatest change in PROMs was between baseline and 3 months.

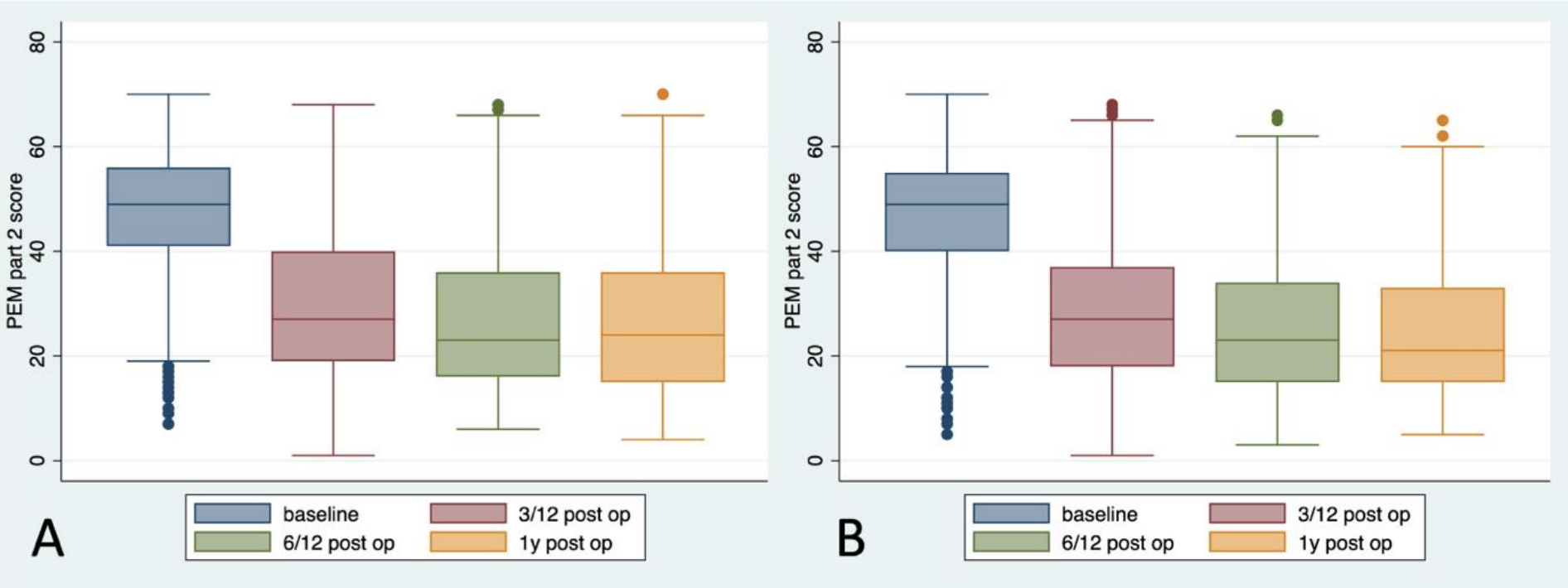


Figure 5.3. Box and whisker plot of the PEM part 2 score following a) trapeziectomy, and b) trapeziectomy plus LRTI
where the box represents the interquartile range, the line within the box is the median, and the whiskers represent 1.5 times the IQR above the 75th percentile, and 1.5 times the IQR below the 25th percentile.

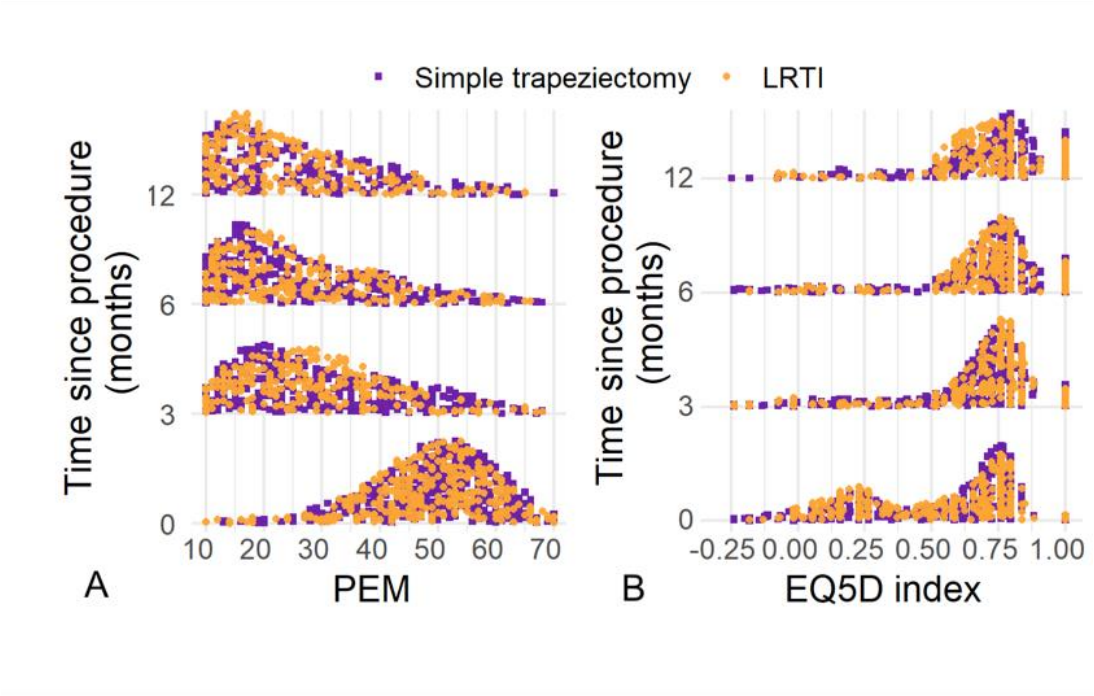


Figure 5.4 Histogram of both PROMS at baseline and 3, 6, 9 and 12 months post operatively

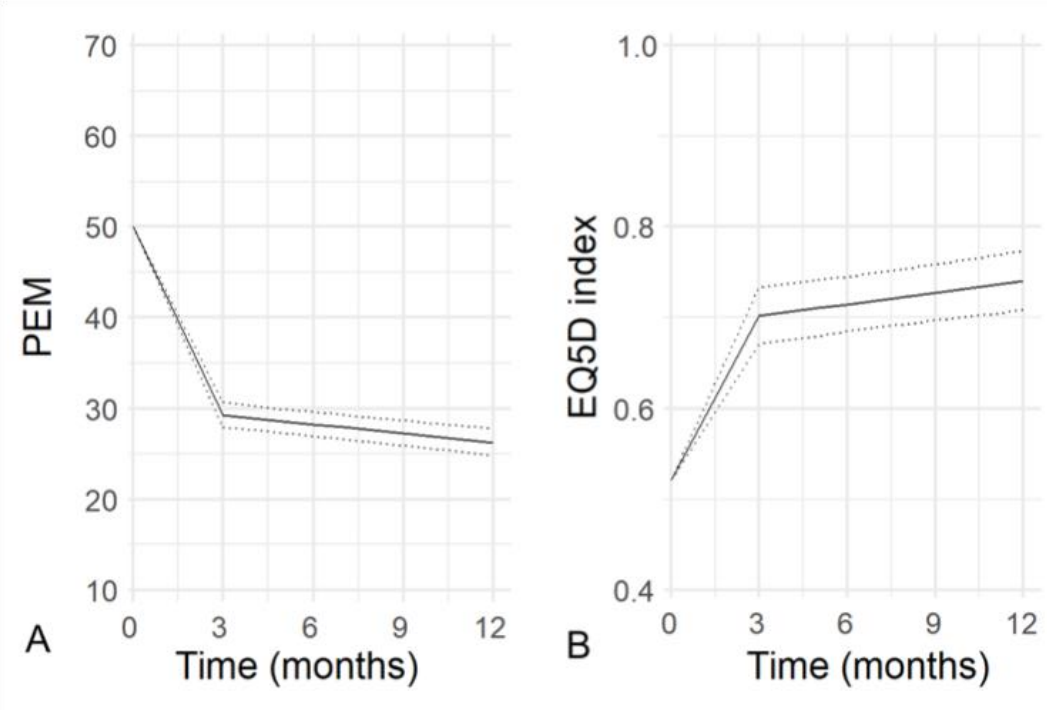


Figure 5.5 Change in EQ5D index and PEM part 2 from baseline to 3, 6, 9 and 12 months post operatively

Table 5.4 Mixed effects regression model coefficients

	Post-operative PEM part 2 score		
Predictors	*Estimates*	*95% CI*	*p*
Baseline PEM part 2 score	0.31	0.23 – 0.40	<0.001
Sex: Male	2.55	0.31 – 4.80	0.026
Age	-0.22	-0.32 – -0.12	<0.001
Procedure: Trapeziectomy compared with LRTI	-0.40	-2.22 – 1.42	0.665
Time	-0.33	-0.45 – -0.21	<0.001
	Post-operative EQ5D index		
Predictors	*Estimates*	*95% CI*	*p*
bs(age, 3)2	0.59	0.26 – 0.92	<0.001
bs(age, 3)3	0.55	0.08 – 1.03	0.023
bs(eq5d_index_baseline, 3)1	1.22	0.94 – 1.50	<0.001
bs(eq5d_index_baseline, 3)3	1.05	0.88 – 1.22	<0.001
Procedure: Trapeziectomy compared with LRTI	-0.00	-0.03 – 0.03	0.806
sex: Male	-0.05	-0.09 – -0.01	0.010
bs(age, 3)1	0.73	0.03 – 1.43	0.042
bs(eq5d_index_baseline, 3)2	0.47	0.33 – 0.61	<0.001
time	0.00	0.00 – 0.01	<0.001

5.5 Discussion

5.5.1 Key findings

This study found that there was an improvement in PROMS following surgery in both a generic quality of life and a hand focussed measure in routine clinical practice.

In this study the improvement in PEM was 23 out of a total of 77.Considering the magnitude of this change, I think this represents a meaningful change for patients. The mean change in EQ5D index was also substantial at 0.21 at one year and compares favourably to other nationally collected PROMS. The improvement seen is greater than quoted for hernia repair (0.081) and varicose vein surgery (0.093), but less than is seen with hip or knee arthroplasty (0.35-0.45). [136, 186, 187] Whilst there was a meaningful difference following surgery, there was no statistically or clinically significant difference in outcome between two procedures.

Methodologically, UKHR is light on content, but has some information that adds to the literature in the clinical field. Without further surgical or demographic information it is difficult to identify confounding by indication, selection bias or draw more meaningful conclusions that may otherwise be possible with linkage to EHR data, or an administrative data source

5.5.2 Strengths and Limitations

The strength of this study lies in its comparison of the two major surgical techniques for BTOA in routine clinical practice, making results more generalisable and outside the controlled setting of an RCT. There is an increasing trend in the use of routinely collected data in making pragmatic healthcare funding decisions, and therefore this work adds to the current evidence surrounding interventions for BTOA.[18] There are currently few registries and datasets specific to hand surgery internationally, in addition to the fact that surgical cultures in some countries is heavily weighted towards LRTI reconstruction. This therefore means that few studies can compare trapeziectomy and LRTI in routine practice. [92, 109, 111]

Unfortunately, this work cannot comment on other surgical subtypes, non-operatively managed patients, or how the decision to proceed to surgery was made.[188-192] The study does not assist in our understanding of whether patients would improve irrespective of surgery and tells us little other demographic or disease information. For example, it cannot tell us about the incidence of post traumatic BTOA, comorbidities or prior treatment undertaken. Most importantly input into the UK Hand Registry is voluntary, carrying the selection bias of those surgeons engaged with an evidence-based practice entering their

patients. It also contains a very small proportion of UK clinical practice, which is identified when contrasting the number of BTOA surgeries undertaken in the NHS in England identified in chapter 4. Finally, whilst PEM is of use in the UK, the rest of the world tends to other upper limb PROMS such as the Michigan Hand Questionnaire and the DASH score.[193, 194] This therefore makes comparing results in this study difficult with international datasets.

There is a gradual attrition in completed PROMS over the post-operative period and this must be acknowledged as a limitation through loss to follow up. In order to identify if loss to follow up was due to poor surgical outcomes, interrogation of those who did and did not complete post-operative PROMS was undertaken with no difference identified in their characteristics. There is no financial incentive to contribute to the UKHR unlike other musculoskeletal registries, but it should be noted that follow up here is slightly better than quoted nationally. The potential risk of bias in this study is therefore equivalent or less than in other areas of surgery, where baseline collection of PROMS is lower than in this study, and the response rate for pre- and post-operative PROMs for hip arthroplasty is quoted at around 56-58%; the response following abdominal hernia repair even lower at 23-29%.[136]

5.5.3 Comparison to other studies

This study concurs with prior systematic reviews of the literature surrounding BTOA surgery and with RCTs that have compared outcome between trapeziectomy and LRTI. [90, 95, 96, 98] However, it has found greater improvement in post-operative PEM part 2 compared to those seen after long term follow up after RCT in BTOA and compared to the MCID following surgery for Dupuytren's disease.[185, 195] In comparison to the previous literature investigating

change quality of life following BTOA surgery, this work adds new evidence to the literature. Yeoman et al reported EQ5D improvement at 2 years, there was no exploration of trajectory over the post-operative course and the main Cochrane review of BTOA surgery included no studies measuring quality of life.[98, 121] Other studies described quality of life following surgery, but without the use of a formal measure like EQ5D.[122, 123]

The main improvement in both EQ5D index and PEM part 2 score was seen in this study in the first 3 months post operatively. A similar trend in seen following wrist fracture, where the majority of improvement in the DRAFFT trial was seen between baseline and 3 months, with the trajectory of improvement set at this stage.[196] This concurs with other areas of orthopaedic surgery where the largest improvement in EQ5D is seen in the first few post-operative weeks in patients sustaining hip fractures, with little improvement after four months.[197] Extension of follow up to several years also does not show a significant change in reported general quality of life in comparison to one year post operatively for elective hip arthroplasty and resurfacing arthroplasty.[198]

5.5.4 Future research

Future work could focus upon comparison of trapeziectomy and LRTI with other more advanced techniques used in the treatment of BTOA using routinely collected data. Results from chapter 4 suggest that techniques such as arthroplasty have higher rates of revision surgery in comparison to more traditional techniques, and therefore greater information surrounding the impact of these techniques upon PROMs would be useful to identify their role in the surgical management of BTOA.

Whilst the results are anonymised and multicentre, distributed around the UK, mandatory inclusion of all patients in the registry would prevent the risk of selection bias. Mandatory inclusion would also align well with the agenda of increasing openness of surgical outcomes in the UK and would improve the generalisability of UKHR research.

Further work could also focus on the role of PEM Part 2 in evaluating hand symptoms and function in BTOA. Extrapolation of the MCID from Dupuytren's disease is useful to compare results produced here to another elective hand surgical condition, but work to establish a the minimal clinically important difference and minimally clinically important change in PEM part 2 for BTOA would enable this work to be more meaningfully placed within the established literature.

6. Systematic Reviews

The risk factors associated with the development of BTOA, and female hormonal risk factors associated with the development of CTS

Contributions: All work in this chapter was designed, conducted and analysed by myself apart from: section 6.3.1 search terms were generated in collaboration with Ms Eli Harriss and Ms Catherine Hartley (Bodleian Health Care Libraries, University of Oxford). Ms Kari Shah acted as second reviewer for the BTOA study and Mr Ryan Lam acted as second reviewer of abstracts and full texts in addition to undertaking second reviews of data quality and risk of bias assessments with second look data extraction for the CTS study. Ms Hayat Nadama and Ms Somy Charuvilla acted both as second reviewers of abstracts and full texts in addition to undertaking second reviews of data quality and risk of bias assessments alongside second look data extraction.

6.1 Summary

This chapter aimed to systematically appraise the literature for risk factors associated with BTOA and CTS prior to undertaking in depth risk factor association studies using prospective cohort studies and in a federated network analysis. The BTOA systematic review evaluated the role of any risk factor in disease development, but due to the large evidence base for CTS the review was focussed upon the area of female hormones. This chapter compares the

two systematic reviews, highlighting the areas of similarity and differences both in the available literature and the risk factors identified.

Strong evidence was found for the association of aromatase inhibitors (AIs) and the association of pregnancy with increased CTS incidence, whilst strong evidence was found for an association with female sex, increasing age, body mass index (BMI) and increased bone mineral density with BTOA development. Strong evidence was also found for an association of BTOA with genetic polymorphisms and for there being no association with physical activity.

6.2 Introduction

In the first part of this thesis, demographic trends in the incidence of carpal tunnel decompression (CTD) and surgery for BTOA in England were identified from a bespoke HES APC extract. These trends have shown a peak in the incidence of surgery in the perimenopausal period, and this peak in incidence has been previously reported in smaller cohorts in the US and Italy, and within CPRD in the UK. [49-51] Whilst there is traditional clinical teaching that these conditions are known to be more prevalent in women, the majority of evidence for these statements taken from samples of patients with symptoms or from cross-sectional studies without further qualification. [46, 48]

Similarly, there is evidence in the literature that hand OA is two separate entities: BTOA and digital or interphalangeal joint (IPJ) OA.[34-36] It therefore felt pertinent to undertake a specific

review of the literature of BTOA in isolation from hand osteoarthritis (HOA) to better inform future risk factor association studies.

The clinical aim of this study was to identify important risk factors associated with the development of CTS and BTOA in the literature. Due to the breadth of literature found upon initial scoping review for carpal tunnel syndrome and due to the clinical focus of Chapters 7 and 8 being upon the influence of female hormones on disease incidence, the CTS systematic review focussed upon female hormonal factors only.

The methodological aim of this chapter was to undertake a systematic review of aetiology to gain greater expertise in using this technique in observational literature and of how to lead more junior colleagues through the blinded review process.

6.3 Methods

Both studies used the PECOS (population exposure comparison outcomes study) framework to develop the study question and design, and were registered with the PROSPERO prospective register of systematic reviews.[199-201] Both studies were developed in line with the PRISMA statement for systematic reviews.[202] The BTOA study was undertaken as part of a wider systematic review of factors associated with development and progression, but since the risk factor association studies in Chapters 7 and 8 focus upon incident disease rather than progression, only the work associated with BTOA disease development is discussed in this chapter.

6.3.1 Study strategy

A bespoke strategy based upon Boolean logic with search terms identified from index and free terms was used. Search terms were generated uniquely for each included database and in collaboration with Eli Harriss and Catherine Hartley (Bodleian Health Care Libraries, University of Oxford). A full list of search terms used are given in Appendix E Tables E.1 and E.2. Data deduplication was undertaken electronically.

6.3.2 Databases included

Electronic searches were undertaken in MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present; Embase (from 1974); PsycINFO (1806 to present); AMED (1985 to August 2019); CINAHL; Cochrane Library (Issue 8 of 12, August 2019); Web of Science (SCI-EXPANDED & CPCI-S) 1945-present. The search for CTS was undertaken on 06/08/2019 and the search for the BTOA study was undertaken on 24/09/2020.

6.3.3 Inclusion Criteria

For CTS, any studies that evaluated the relationship of any female hormonal risk factor to the development of CTS were identified. For BTOA, studies that evaluated the relationship of any risk factor (demographic, biochemical) to the development of BTOA were identified. The focus was upon identifying studies with higher levels of evidence, with case reports,

letters and opinion pieces excluded. A full list of inclusion and exclusion criteria are given in Table 6.1.

In order to restrict the included studies to those dealing with BTOA alone, as opposed to generalised hand arthritis or generalised osteoarthritis, I decided that BTOA must be defined as a single outcome within the study to be included in the review. Articles that included hand osteoarthritis as an outcome were included at title and abstract review stages, and only if at full text review there was no mention of BTOA in isolation was a study excluded. By comparison, the CTS study did not have difficulty since the disease definition is relatively discrete. Whilst CTS can be an acute complication associated with wrist fracture, the aim of this review was to determine factors associated with the development of chronic CTS, and CTS definition did not require further refinement.

Two reviewers independently appraised the search results using the Rayyan software platform.[203, 204] For CTS, titles and abstracts were screened against the criteria in table 6.1 by JL and RL; for BTOA, this was undertaken JL, KS, SC and NH. Full text review was undertaken by two independent reviewers. Discrepancies were resolved by discussion with a third author (DF – primary supervisor).

	Factors associated with development of BTOA	Female hormonal factors associated with development of CTS
Participant	All adults over 18 years	
Exposure	Any variable which has been assessed as a potential risk factor for the development or progression of BTOA- for example, demographic, clinical, genetic risk factors	Any variable which has been assessed as a potential female hormonal risk factor for CTS- for example endogenous factors (parity, age at menarche, age at menopause, breastfeeding) and exogenous factors (use of drugs containing female hormones, or agents blocking female hormones such as contraceptives, menopausal replacement therapy, agents used in the treatment of female cancers such as tamoxifen)
Comparator/Control	Patients who do not display development of disease through imaging or clinically as defined by the individual studies	
Main outcome	One or more of the following: -Clinical criteria- for example, ACR Classification -Radiographic criteria- for example Modified Eaton & Littler, Kellgren-Lawrence, OARSI Atlas, Verbruggen-Veys, Kallman -Need for intervention (intra-articular injection, surgery) Measure of effect is relative risk, odds ratio, risk difference.	Development of CTS using one or more of the following: neurophysiology, clinical examination, or the incidence of intervention (such as using a splint, steroid injection, or surgery). Measure of effect is relative risk, odds ratio, risk difference.
Study criteria-exclusions	Animal studies Cadaver studies Publication not written in English where translation is not available Case reports, abstracts, letters to editor	
	Generalised arthritis studies where BTOA results were not reported separately or provided on request by the author within 14 days, or are grouped within Hand Osteoarthritis without further clarification of anatomical site	

Table 6.1 Study design using PECOS framework

6.3.4 Analysis

6.3.4.1 Data extraction

Once a finalised list of included studies was made, a data extraction tool was generated. For both studies, data extracted included the risk factor analysed, the population studied including baseline demographics such as age, sex, worldwide geographical location, date study undertaken; the study follow up time and any loss to follow up; the outcome measured and the measure of effect used, and the results of the study.

6.3.4.2 Quality of evidence & risk of bias

Level of evidence generated by a study was assigned using the Oxford Centre for Evidence Based Medicine levels of evidence.[205, 206] Evidence was assessed for risk of bias using the NIH quality assessment tools depending for cohort, cross sectional and case series studies to give a rating of 'good', 'fair' or poor'.[207] For randomised control trials the Cochrane RoB2 tool was used.[208, 209]

6.3.5 Data synthesis

Simple descriptive statistical analyses were generated. This included patient demographics, the primary outcome and the exposure of interest. Where possible, the risk (as a percentage) or risk ratio was described for each study. For CTS, risk factors were further grouped into exogenous female hormonal factors and endogenous factors.

To synthesise further, an assessment of heterogeneity was undertaken according to Cochrane Collaboration guidelines.[210-212] Risk factors identified were grouped together, and

then divided into those giving consistent evidence (i.e. over 75% of studies included reported the same direction of effect) or mixed evidence (less than 75% of studies included reported the same direction of effect). Consistent evidence was then rated according to the NIH quality assessment tool results of included studies. If there were two or more 'good' quality studies included, it was considered to be strong evidence; if two or more fair or poor quality studies or one good quality study was found it was considered moderate evidence; limited evidence with a low risk of bias was defined by one poor quality study, and limited evidence was defined as including two fair or poor-quality studies.

6.3.6 Meta-analysis

A meta-analysis was planned if two or more studies were considered homogenous. This was planned using RevMan5 to undertake a direct comparison analysis to calculate relative risk ratios using the Cochrane-Mantel-Haenszel test. A random effects model and I^2 statistic was planned to determine heterogeneity and significance set at 5%.

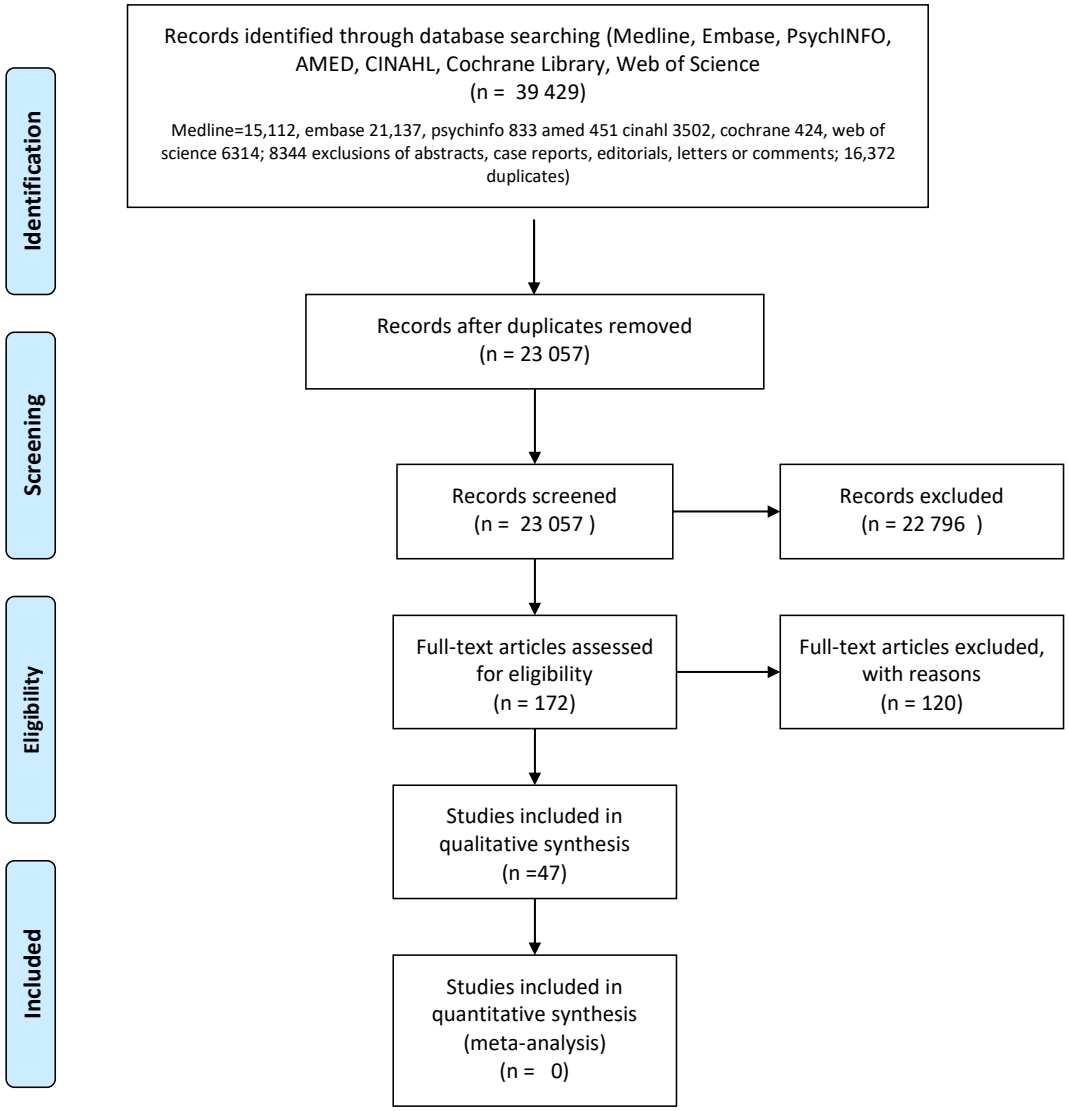
6.4 Results

6.4.1 Study selection

After identifying over 14,000 studies for BTOA and 23,000 studies for CTS, less than 50 studies were included in each systematic review (Figures 6.1 and 6.2).

For BTOA, 93 studies were excluded due to not meeting criteria for identifying BTOA in isolation, or of being too low quality. For CTS, 120 studies were excluded due to lack of

appropriate study design or quality. Included studies in either review were too heterogeneous for meta-analysis and therefore a narrative synthesis was undertaken.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 6.1 CTS Study PRISMA flow chart

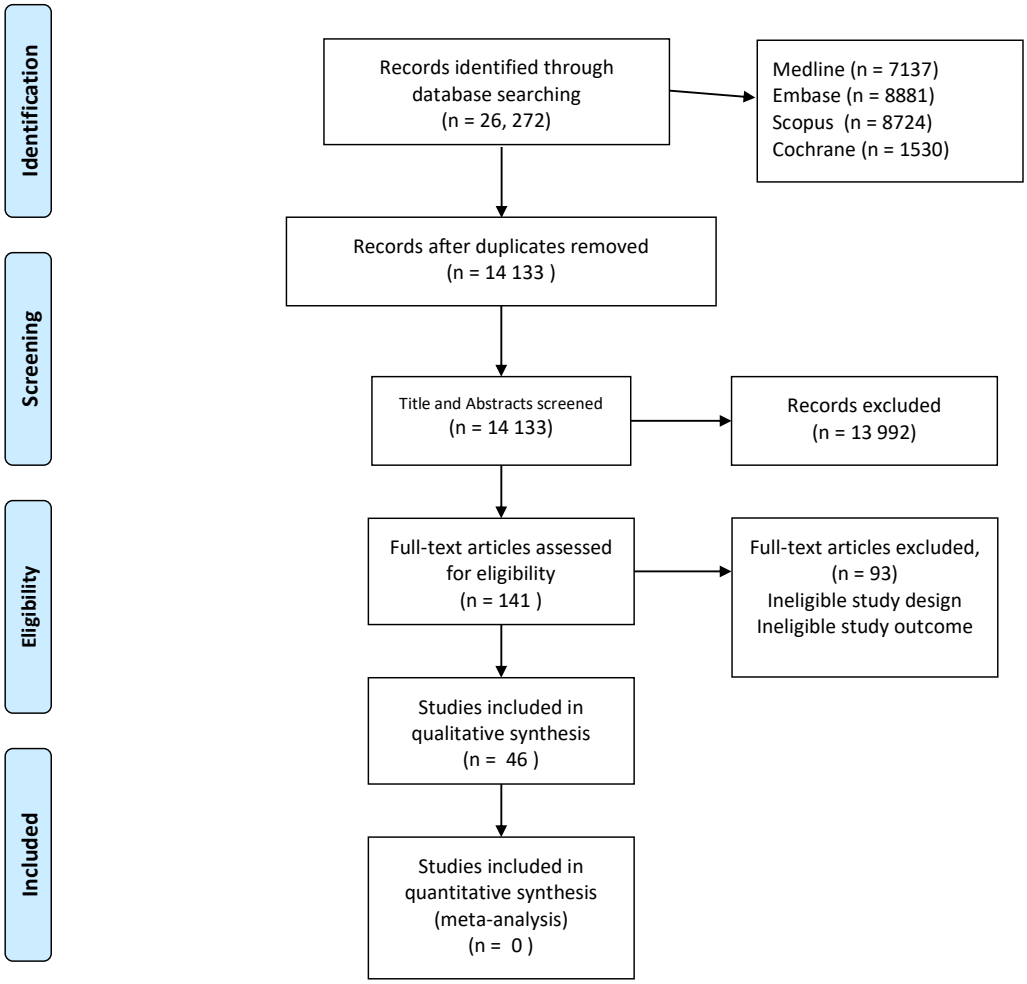


Figure 6.2 BTOA study PRISMA flow chart

6.4.2 Study characteristics

6.4.2.1 CTS

This search identified 3 international RCTs generating 5 level 2 studies (2 post trial studies purely focussed upon CTS) upon the association of aromatase inhibitors with incident CTS. One nested case control analysis was undertaken within one region of general practice

research database (GPRD) and investigated multiple hormonal factors. Two studies used prospective observational cohorts outside of electronic healthcare records to investigate the role of contraception. In total, 11 included studies were considered level 2 evidence, with nine studies being level 3 and the rest assessed as level 4.

3 RCT studies were internationally based, with clear research groups generating evidence in Italy (n=6) and Turkey (n=3). The most common country of origin was the UK (n=9), with the most common region being North America (n=9) followed by Europe aside from Italy and Turkey (n=8), two from Iran, two from Asia and one each from Brazil and Australia.

Most studies used a case definition of carpal tunnel syndrome (CTS) rather than carpal tunnel decompression (CTD, n=3); only the GPRD study investigated the association of risk factors with both CTS and CTD. 14 studies defined CTS after clinical examination, 13 used self-reported symptoms and questionnaires; 11 used a combination of clinical and neurophysiological diagnosis, and 6 used coding in administrative data sets or healthcare records to identify cases. 1 study identified cases based upon receipt of workers compensation for CTS. 17 studies were considered of good quality/low risk of bias, 17 fair quality/moderate risk of bias and 13 of poor quality (Appendix E Tables E.3 and E.4)

6.4.2.2 BTOA

In contrast to CTS, most studies were either cross-sectional (n = 25) or cohort (n = 14) studies, with only 4 case-control, 1 GWAS (genome wide association study), one case series and one twin study. The USA was the most common country of origin (n=15) followed by the UK (n=10) and Europe (n=10) , with only 5 from Asia, and one from both Australia and

Saudi Arabia. Over half of the included studies (n=25) were assessed as being level 2 evidence, 15 were level 3 and 6 were level 4. The majority of studies used radiographic criteria to identify BTOA, with only 9 using combined clinical and radiographic criteria, 3 identified the development of BTOA using a clinical definition and one used diagnostic codes to interrogate an administrative dataset. Overall, most studies were of good quality (n=24), 14 fair and 7 poor quality. The GWAS was exempt from this form of risk of bias assessment (Appendix E Tables E.3 and E.4).

6.5 Risk factors

6.5.1 CTS

Table 6.2 summarises the evidence found. Whilst better quality evidence was available for CTS than for BTOA development, it was difficult to find a common message within the literature for most risk factors. This may reflect the high number of confounding factors associated with the impact of female hormones on disease aetiology.

Strong evidence was found for the association of aromatase inhibitors (AIs) and the association of pregnancy with increased CTS incidence, with limited evidence suggesting an association with breastfeeding with increased CTS incidence during the puerperium. All other factors did not meet *a priori* criteria for evidence consistency and direction of effect. Full data extracted is given in (Appendix E Table E.5).

Table 6.2 Summary of risk factors identified for development of CTS

Association	Total number of studies identified	Strong Evidence	Moderate Evidence	Limited Evidence	Mixed Evidence
Exogenous					
Aromatase Inhibitors	9	4+	3+	2+	
OCP	7				7
HRT	7				7
BSO/Hysterectomy	6				6
Endogenous					
Pregnancy	16	3+	7+	6+	
Parity	13				13
Age at pregnancy	3				3
Menopause	6				4
Age at menopause					2
Breastfeeding	2			2+	

BSO= bilateral salpingoophorectomy; OCP= oral contraceptive pill
+ = positive association between risk factor and development of CTS
| = no association between risk factor and development of CTS
- = negative association between risk factor and development of CTS

6.5.1.1 Strong evidence

-Aromatase inhibitors

Three RCTs (IBIS II, ATAC, IES) investigated the incidence of a clinical diagnosis of CTS as a secondary outcome of hormonal treatment for breast cancer. In IBIS II (International Breast cancer Intervention Studies) trial of anastrozole (a non-steroidal AI) versus placebo for post-menopausal breast cancer, an odds ratio of 2.16 for a clinical diagnosis of CTS [1.4-3.33] was seen for those treated with anastrozole, which increased to OR 3.06 [1.21-7.71] for CTD surgery.[213, 214] The odds of developing clinical CTS were even higher in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in post-menopausal women with early breast cancer, with an OR 3.55 [2.2-5.92] for those receiving anastrozole compared to tamoxifen (6186 women equally divided).[125, 215] Similar results were also found in the Intergroup

Exemestane Study (IES) for postmenopausal women with early invasive breast cancer, where an OR 5.32 [2.39-11.49] of clinical CTS in those receiving exemestane (a steroidal AI) rather than tamoxifen was found.[216] As tamoxifen is known to have a partial oestrogen agonist effect, anastrozole being a competitive antagonist (type 2 AI) and exemestane being a steroidal, full irreversible blockade of oestrogen production peripherally (type 1 AI), these studies point towards the oestrogen deficiency being associated with development of CTS. Studies with lower levels of evidence concurred with these RCTs. Laibidi *et al.* followed post-menopausal women taking AIs and tamoxifen. They found that CTS was only diagnosed in those take took AIs and this side effect was a driver for some women to switch to tamoxifen.[217] Symptoms were found to be worst between baseline and 3 months of treatment initiation in another case series by Sheng *et al.* with two other case series identifying CTS as the main musculoskeletal side effect diagnosed after initiating AI treatment. [218-220]

-Pregnancy

16 studies investigating CTS originating in pregnancy were found, ranging from 14,579 pregnancies followed in the Rochester Epidemiology project observational primary care study in the US, to single cohorts of pregnant women presenting with CTS in primary and secondary care centres in France, Malaysia, Australia, the Netherlands, Norway, Iran, Italy, Brazil and Turkey.[47, 221-235] The majority of studies followed the natural course of the disease only. The timing of CTS onset within pregnancy was variable, but predominantly began in the third trimester, with prevalence ranging from 2% to 34%. The majority of cases resolved spontaneously after birth. Malay ethnicity was found to be associated with increased CTS incidence, but there was mixed evidence for the interaction of weight gain and parity upon

the risk of disease development.[226, 235, 236] Those developing CTS had a higher incidence of 'arthritic symptoms' pre-pregnancy, and pre-eclampsia.[227] Development of oedema was suggested as a risk factor in two studies, with only increasing fluid retention associated with reported CTS symptoms when adjusted for age, BMI, parity and depression scores in one Dutch study.[47, 231]

6.5.1.2 Limited evidence

-Breastfeeding

Only two studies were found to discuss the role of breastfeeding, and even in these studies, the natural course of CTS in breastfeeding versus non breastfeeding mothers was studied. [54, 226] Both studies suggested that resolution of pregnancy onset CTS was more likely and quicker in non-breastfeeding compared to breast feeding mothers, with the suggestion that CTS resolution only occurred with cessation of breastfeeding. Compared to mothers who were breastfeeding, the odds ratio of pregnancy onset CTS resolution was 1.7 for women not breastfeeding within the first six months postnatally.

6.5.1.3 Mixed evidence

-Parity

Thirteen studies investigated the role of parity in CTS incidence, but the consistency of the reviewed literature was very mixed with five papers suggesting increased CTS associated with an increasing number of births, five suggesting no association and three suggesting reduced incidence. Some studies focussed upon CTS occurring during pregnancy and some

on CTS incidence in later life, but this difference of disease definition cannot fully explain the difference in results found.

The strongest evidence came from three large observational studies the UK and US.[225, 237, 238] Wright *et al.* found an increased incidence of CTS diagnosis associated with increasing parity (live birth number 2 or 3 OR 1.22 [1.05-1.75]) in a large hospital based US electronic healthcare record (EHR) cohort of 17,623 pregnant women presenting for prenatal visits, but larger relative risks were seen associated with pre-pregnancy obesity, higher levels of education and number of prenatal care visits.[225] Conflicting evidence was generated by two nested case control studies within UK general practice based cohorts predominantly studying contraception use, where both no association and an increased incidence of CTS was associated with parity.[237, 238]

Case-control studies of women presenting with clinical CTS in Turkey, France, Germany, and in three studies from Italy all found a greater number of pregnancies compared to controls, whereas a study of perimenopausal women scheduled for CTD in Korea found no association with parity. [239-245] One further cross-sectional analysis of CTS during pregnancy suggested there was no association with increasing parity, but an association with increasing maternal age.[246]

-Oophorectomy, hysterectomy and menopause

An association between hysterectomy and oophorectomy with CTS has been found in case control studies, with a greater association between clinical CTS presentation shortly after menopause. Work by De Krom *et al.* in the Netherlands found an OR of 2.32 for menopause

in the previous year and OR of 1.78 for hysterectomy in those with a CTS diagnosis compared to healthy age matched controls, with no association found with general menopausal status, age at menarche, age at menopause, parity, gestational DM, OCP use in the last 5 years.[42] Similarly, Pascual *et al.* found a relative risk of 4.25 [1.47-12.61] for a clinical diagnosis of CTS when comparing women who had undergoing oophorectomy compared to healthy controls, with increased risks found in other case control studies in the US and Germany.[247-249] Nested case control analysis within the prospective twin registry study by Hakim *et al*. also found increased incident diagnosis of CTS associated with self-reported perimenopausal (OR 1.53[1.01-2.32]). The association of CTS diagnosis with hysterectomy and postmenopausal status (post menopause 1.43 (0.89-2.29) was not significant after adjusting for menopausal status (OR 1.12 [0.67-1.13]).[250]

By contrast, no association was found between CTS and hysterectomy or oophorectomy in a further 2 case control studies.[244, 245] Conflicting evidence surrounded the impact of age at menopause, with three studies reporting either a positive, negative or no association with development of CTS.[42, 245, 251]

-HRT

The Women's Health Initiative compared the impact of HRT in post-menopausal women versus placebo upon the incidence of CTS in 2 double blinded RCTs. A protective effect of both oestrogen alone and combined oestrogen and progesterone HRT for those without hysterectomy was found.[252] This study concurs with an early case series by Hall and Spector that noted reduced CTS incidence with HRT use, but conflicts with 5 further case control studies that saw an increased incidence in women taking HRT.[62, 77, 242, 248, 253-255]

-OCP

Conflicting evidence for the association of oral contraceptives (OCP) with CTS was found. The Ox-FPA contraceptive cohort study examined the risk factors associated with CTS in young British Caucasian women, and found no association of OCP use if aged under 45, but an increasing referral rate associated with longer previous OCP use.[238] The Royal College of General Practitioners Oral Contraception study (RCGP OCP) in UK general practice investigated the association between past combined oestrogen and progesterone OCP use and CTS diagnosis either in primary or secondary care. Past combined OCP use was associated with CTS diagnosis in univariable analysis, but was not associated multivariable analysis.[237] More recently a nested case control study using a region of the general practice research datalink (GPRD) noted that current or past combined OCP use was associated with reduced rates of CTS diagnosis (OR 0.82[0.71-0.95]) within multivariable analysis, with a similar odds ratio but not statistically significant relationship seen for the association with carpal tunnel decompression surgery.[77] This may be due to the small numbers of surgical cases found. Similar results were found by in a small case control study of US factory workers, but this conflicted with increased rates found in OCP users in the two previously mentioned case control studies by Ricco *et al.* and no association in factory workers in France.[242-244, 248]

6.5.2 BTOA

Table 6.3 summarises the risk factors identified for the development of BTOA, and the strength of the evidence found. Strong evidence was found for an association with female sex, increasing age, body mass index (BMI) and increased bone mineral density. Strong

evidence was also found for an association with genetic polymorphisms and no association with physical activity. Moderate evidence was found for an association with Caucasian ethnicity, diabetes mellitus and hand OA, but mixed evidence for the association with knee OA and joint instability. A more in depth data extraction table can be viewed in Appendix E Table E.6.

Table 6.3 Summary of risk factors identified for development of BTOA
(modified from work by Hayat Nadama)

	BTOA Development					
Factor investigated	**Total Number of Studies Identified**	**Strong Evidence**	**Moderate Evidence**	**Limited Evidence with low risk of bias**	**Limited Evidence**	**Mixed Evidence**
Demographics						
Sex	8	8+ Female Sex				
Age	7	7+ Increasing Age				
Ethnicity	5		3+ Caucasian compared to African American	1+ Caucasian compared to Chinese	1+ Caucasian compared to Japanese	
Education	2		2 |			
Genetic	9	9+				
Lifestyle						
Smoking	1				1 +	
Alcohol	1				1 + Men	
Hand function						
Grip Strength	1			1+ Men		
Physical Activity	5	5 |				
Joint Instability	4					4
Hand Dominance	2					2
Cardiovascular						
Metabolic Syndrome	2					2
Hypertension	1			1 |		
Diabetes Mellitus	2		2 |			
BMI	4	4 + Increasing BMI				

Cardiovascular Disease	2		2 |			
Musculoskeletal disease						
Bone Mineral Density	2	2+ High BMD				
Distal Radius Fracture	*1*				1	
Association with OA in other locations	7		4 + hand OA		2 | hip OA 1 | foot OA	4 knee OA
Other						
Cerebral Palsy	1				1 |	
HRT	1				1 |	
HRT= hormonal replacement therapy + = positive association between risk factor and development of BTOA | = no association between risk factor and development of BTOA - = negative association between risk factor and development of BTOA						

6.5.2.1 Strong evidence

Overall, there was strong evidence for the association of female sex, increasing age, and a genetic component with BTOA. High body mass index (BMI) and high bone mineral density (BMD) were also associated with increased risk of disease, whilst there was strong evidence to suggest no association of BTOA development with physical activity.

-Age and sex

Studies focussed upon associations with age and sex were the most common literature found.[256-262] Many studies focussed upon both age and sex simultaneously. [256-261] Four of the seven studies investigating age found a significant association between increasing age and BTOA even when adjusted for sex.[66, 256, 258-260] The other studies described an increasing BTOA prevalence with increasing age and female sex without further risk factor association studies.[256, 257, 260, 263] Female sex was associated with BTOA development with a relative risk to male sex that could be as high as 4.5 to 1. [256, 258, 259, 261] Whilst overall strong evidence of a positive association with female sex was found, a further two studies found no association of BTOA development in one prospective cohort study from the US and one cross sectional study from Korea.[262, 264] This may reflect a difference in the patients studied, since Cho *et al.* found no association of radiographic BTOA in a sample of community based Koreans aged over 65 years, and the mean age of participants in Snyder *et al.*'s prospective cohort being 70 years. This may suggest an interaction between age and sex, with BTOA development at a younger age associated with female sex.

-BMI

Four of the studies that identified the association of age and sex with BTOA development also investigated the role of BMI.[66, 256, 258, 259] Increased BMI was associated with an increased risk of BTOA in three of the studies, with Wilder *et al.* noting that increased BMI was only associated with increased incidence in women. A nested case control study in Germany suggested that BMI was not an independent risk factor in multivariable analysis after adjustment for age, sex, activity within occupation and OA at other anatomical sites.[258] These studies emphasise the complexity of investigating the role of obesity in disease aetiology and the interplay of many factors that may be behind an increased prevalence initially reported.

-Genetic associations

Genetic variants associated with BTOA development and heritability were the second most common focus in the literature. [265-273] Seven candidate genes were implicated in BTOA development, with the strongest evidence in support of the *ALDH1A2* variant in both Icelandic and US based studies.[267, 270] The Icelandic GWAS by Stryrkarsdottir *et al.* identified this variant as associated with severe hand OA, with other studies suggesting links to oestrogen receptors (ESR1, ESR2) interleukins (IL-4, IL13) and matrilin 3, an extracellular matrix protein in BTOA disease development that were not replicated in this cohort.[266, 268, 269]

Positive heritability for BTOA was identified in sibling studies, with an OR of 2.6 for site sharing in siblings with familial OA.[272] Heritability of BTOA is estimated to be 68% in twin

studies, with the kinship coefficient of heritability higher for family members with more severe radiographic disease [265, 271, 272]

-Physical Activity

This overarching term includes studies investigating the role of manual labour in occupation, and one study that investigated the role of chopstick use in BTOA development in a Chinese population.[66, 259, 274, 275] Overall, strong evidence for no association was found in the literature. Work by Fontana *et al.*, suggested an association with repetitive movements in female factory workers, but manual occupation or 'physical exertion' was not found to be associated with BTOA development in two cross sectional studies in Germany and the UK or a Finnish cohort study representative of the general population.[66, 258, 259, 274] a negative association with the prevalence of BTOA was also found with chopstick use in the study by Hunter *et al.*[275]

-Bone mineral density

High bone mineral density was found to be associated with increased incidence of BTOA in two studies from the UK, investigating the potential association of high BMD with obesity.[276, 277] Hart *et al.* in the Chingford prospective cohort study identified an association of increased lumbar and hip BMD in women with BTOA, and work by Gregson *et al.* suggested an increased incidence of BTOA in men and women with elevated BMD in comparison to family controls.

6.5.2.2 Moderate evidence

Moderate evidence was found an association of BTOA development with IPJ hand OA, and Caucasian ethnicity in comparison to African American ethnicity. [66, 262, 263, 278-283] Moderate evidence also supported no association with education level, diabetes mellitus and cardiovascular disease. [66, 258, 259, 284-286]

-Ethnicity

Moderate evidence was found for a positive association of Caucasian ethnicity and BTOA development compared to African-American heritage, with limited evidence for an increased risk of BTOA with Caucasian heritage compared to Chinese or Japanese ethnicity.[262, 263, 281-283] Studies comparing Caucasian and African American ethnicity in the US found a twofold increased risk in those with Caucasian heritage, with cross-sectional studies in China and Japan presenting a three to ninefold risk of BTOA prevalence in participants of Caucasian ethnicity compared to those of Chinese and Japanese ethnicity respectively.

-Hand OA

A positive association was found in four studies for concomitant hand IPJ OA in BTOA development. [66, 278-280] This included risk factor association studies that persisted after adjustment for age and sex.[66]

-Education

Two studies included in the review investigated the association with education level, and no association was found with BTOA development. [66, 259]

-Cardiovascular disease and Diabetes mellitus

Moderate evidence was found in this review for the association of cardiovascular disease and diabetes mellitus upon BTOA.[66, 286] Hoeven *et al.* found no association with atherosclerosis in multivariate analysis including adjustment for age and BMI, that concurred with work by Haara *et al*. Similarly, moderate evidence showed no association of BTOA with diabetes mellitus.[66, 258]

6.5.2.3 Limited and Mixed evidence

Limited evidence was found for the role of hypertension, grip strength, smoking and alcohol, cerebral palsy, HRT use and other musculoskeletal disorders (distal radius fracture, hip and foot OA). [66, 256, 258, 278, 287, 288] Mixed evidence was found for the association of knee OA, joint instability, hand dominance and metabolic syndrome. [66, 256, 258, 260, 278, 289-295] Further details of these other risk factors are given in the data extraction table in Appendix E. Table E.6.

6.6 Discussion

6.6.1 Key findings

Strong evidence was found for the association of CTS with the use of aromatase inhibitors, and pregnancy. There was limited evidence for the role of breast feeding with increased duration of CTS after pregnancy, with mixed evidence for the role of OCP, HRT, parity and menopausal factors such as type or age at menopause. For BTOA, strong evidence was

found for a positive association of disease development with age, sex, increased BMI and BMD and no association with physical activity.

Methodologically, this review highlights that orthopaedic research remains predominantly focussed within lower levels of evidence and study quality. High quality research in other domains such as cancer can be used to influence musculoskeletal research when they incorporate secondary outcomes of interest. Few papers contained surgically defined disease as the outcome, restricting the value of both systematic reviews in designing my risk factor association studies. Further work is needed in this area of surgical epidemiology, and to identify associations when disease phenotype is most severe.

Undertaking systematic review rather than a scoping review during this programme of work felt important. The process of leading a systematic review and learning the technique involved felt valuable for future work and pertinent to direct the work in MWS and OHDSI, where it would be possible to adjust for known confounders through the rich phenotypic information available. Work in Chapters 3-5 had focussed upon surgical intervention, but the work in Chapters 7 and 8 is focussed upon aetiology. Acknowledging the limitation of time and the inability to systematically appraise both surgical intervention and aetiology for the two hand conditions, the evidence base seemed wider in aetiology and more appropriate for an in-depth approach.

6.6.2 Strengths and Limitations

A systematic approach has enabled a large amount of literature to be appraised. Undertaking two reviews focussed upon the two conditions has enabled comparison between the evidence found. Whilst overarching themes have been identified, the lack of consistency in the literature, especially surrounding hormonal factors in CTS prevents a strong pathophysiological hypothesis to be made. This is particularly true for studies investigating the impact of menopausal factors.

The BTOA literature review focussed upon BTOA specifically rather collecting data including hand OA in order to identify the difference in BTOA aetiology to digital or interphalangeal joint (IPJ) OA. Whilst this enables increased specificity, this review may have lost power or scope due to this. Parallel work focussed upon IPJ OA has been led by a colleague within the department enabling us to work together, but this review would also have the limitation of missing articles that do not give further granularity of hand OA location.[296, 297] The reviews by Shah *et al.* also found an association with increasing age, female sex and higher BMI. Parity was associated with IPJ OA in this work albeit supported by limited evidence. In BTOA parity was found to have mixed evidence of an association, despite the evidence being of higher quality.

6.6.3 Future research

These literature reviews identified interesting gaps in the evidence base, and also identified areas that may not have been obvious due to the focus of my clinical practice in orthopaedics. The difficulty of controlling confounding due to lifestyle factors and the

interplay of multiple female hormonal factors suggests that interesting research focussed upon endogenous female hormonal factors- particularly parity and oophorectomy would be valuable. These factors are best identified in MWS, and this review drove study design in Chapter 7.

In the context of exogenous female hormones, interesting evidence was raised from the breast cancer literature. Strong evidence has been generated from clinical trials, and it was pertinent to explore if this is replicated in routine clinical practice. The 'arthralgia' discussed as a side effect in these RCTs has not been specifically defines to a musculoskeletal diagnosis, such as BTOA. Investigation of both CTS and BTOA alongside each other in a pharmacoepidemiological study could therefore add to the literature to suggest the pathophysiology behind the symptoms.

7. Prospective Cohort Study: Million Women Study

The Association between endogenous female hormonal factors and carpal tunnel syndrome or hand osteoarthritis: a prospective cohort study from the Million Women Study

Contributions: All work in this chapter was designed, conducted and analysed by myself apart from the data extract was generated from the main Million Women Study dataset thanks to Drs Keith Shaw, Sau Wan Kan and Kirstin Pirie. Senior advice was gratefully received from Prof Gill Reeves.

7.1 Summary

This chapter focusses on the possibilities for surgical epidemiological study using a prospective cohort study linked to routine secondary care data. Million Women Study provides rich data around reproductive and menopausal factors that are not routinely collected in administrative data, and through linkage to HES APC offers the opportunity to be used to study surgical hand conditions. This chapter builds upon the work in Chapters 3, 4 and 6 to undertake a more advanced and in-depth analysis adjusting for many confounders. It uses a traditional approach to epidemiological analysis, discussing the strengths and weakness of using prospective cohorts for surgical research.

An increased risk of both conditions was associated with early menarche, an increased number of full term pregnancies, and bilateral oophorectomy. Undergoing oophorectomy at an early age was associated with a 50% increased risk of CTS (1465/64 818 vs 256/7 071 and twice the risk of BTOA (aged <46 years; 184/64 818 vs 41/7 071), with early age at menopause not being significant for those experiencing a natural menopause.

7.2 Introduction

Observed variations in the incidence of carpal tunnel syndrome and hand osteoarthritis around reproductive milestones in women have led to suggestions that oestrogen is implicated in disease aetiology. [52, 298] Both conditions are more prevalent in women, with a peak in incidence in the perimenopausal period.[46, 48, 50, 51, 299] Pregnancy is considered to be 'one of the most frequent physiologic conditions associated with CTS' and HOA has been known to predominantly affect women as 'arthritis of the menopause' from as early as 1925.[47, 48, 52]

Trends seen in CTD in HES APC in chapter 3 saw a large peak in observed surgeries undertaken between the ages of 45-55 in women that was not replicated in men. Similarly, there was a large disparity in the number of procedures undertaken BTOA between men and women in Chapter 4, with a peak in cases around the age of the menopause for women.

Systematic review in Chapter 6 emphasised the strength of evidence surrounding exogenous manipulation of oestrogen.[52, 77, 216, 218-220, 250, 252, 300-303] Oestrogen blockade through drugs such as aromatase inhibitors in cancer therapies has been associated with

increased CTS and BTOA development, with mixed evidence for the role of menopausal hormonal replacement therapy (HRT) and the oral contraceptive pill (OCP) in the two conditions.[62, 77, 238, 242, 248, 254, 255, 304, 305] However, there is very mixed epidemiological evidence on the possible role of endogenous hormonal (reproductive) factors in the development of CTS and BTOA, in part due to the difficulty in studying endogenous hormone production in female life stages influenced by many confounders.[47, 54, 55, 57, 221-227, 229-235, 237, 238, 247-249, 306-308]

The clinical aim of these analyses was to investigate associations between endogenous female hormonal factors (menarche, childbearing and menopause) and incident, surgically significant carpal tunnel syndrome and base of thumb osteoarthritis within a large prospective cohort of UK women, accounting for potential confounding factors.

The methodological aim of this chapter was to join a well-established team who have a great deal of expertise in running a longstanding prospective cohort study. The aim was to better understand how the process of establishing and maintaining a cohort study occurs and the potential issues around this. I also aimed to better understand how to use established prospective cohorts linked to routine data to better understand orthopaedic conditions rather than developing a prospective cohort de novo. I aimed to use this experience to better appraise how established prospective cohorts could be repurposed research data to improve the quality of observational evidence in orthopaedic surgery.

7.3 Methods

This study was undertaken within the Million Women Study (MWS), an established prospective cohort study detailed in Chapter 2.3.[309]

7.3.1 Participants

Analyses were restricted to post-menopausal women to give a firm case definition and to focus on the strengths of the MWS cohort that recruited women aged 50-64 at baseline. Women were considered post-menopausal at recruitment if they reported having had a natural menopause or had undergone bilateral oophorectomy before natural menopause. In addition, women with unknown menopausal status at recruitment were assumed to be postmenopausal if they were aged 55 years or older at recruitment, since 96% of women within MWS with a known age at natural menopause were post-menopausal at this age.[310] Women were excluded from the analyses if they had a prevalent diagnosis of any cancer (as identified from the cancer registry or self-reported in the study) at study recruitment due to the risk of potential confounding from cancer treatment, and differences in the frequency of presentation to medical services, and/or management of musculoskeletal disease. Women were also excluded from each respective analysis if they had a prevalent diagnosis of the outcome CTS or BTOA as identified in HES England and ISD Scotland prior to the time of recruitment to MWS.[128, 142] CTS and BTOA were identified using the validated list of World Health Organisation International Classification of Disease, 10th revision codes (ICD-10) and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS) 4 described in Chapters 2-4 and given in Appendix A Tables A.1 and A.2).[132, 133, 311] Participants were followed from recruitment to first of incident outcome, death, emigration, or the end of the follow-up period for these analyses (31 December 2017).

7.3.2 Exposures

All exposure variables were as reported at study recruitment. In all women, endogenous hormonal exposure variables of interest investigated were age at menarche (categorised into <11, 12, 13, 14, 15, 16, >17 years) and parity status (parous versus nulliparous). In parous women, the number of full-term pregnancies (1, 2, 3, 4+ pregnancies); age at first birth (<20 years, 20-29 years, aged 30 and over), and history of breast feeding (ever/never) were also investigated. Analyses of menopausal factors (natural or surgical via bilateral oophorectomy, age at menopause) were restricted to never-users of hormone therapy for the menopause (HRT) in the main analysis, with age at menopause categorised as <46, 46-48, 49-51, 52-53, >54 years.

Further analysis was undertaken combining age of menopause, and type of menopause (oophorectomy versus natural menopause) to determine the interaction of the two exposures. Additional sensitivity analyses for menopausal exposures of interest were also run within HRT users to further appreciate the potential for residual confounding.

7.3.3 Outcomes

An incident case of surgically treated CTS or BTOA was identified through linked hospital admission records indicating an intervention (surgery or intra-articular injection undertaken in hospital) for CTS or BTOA, again using the validated ICD-10 codes to define diagnoses and OPCS-4 codes to define interventions for each outcome (Appendix A tables A.1-A.2).[311]

These outcomes could occur at any time after recruitment. CTS and BTOA were run as separate outcomes in each analysis.

7.3.4 Statistical Analysis

Multivariable Cox proportional hazards models were used to obtain adjusted hazard ratios (henceforth referred to as relative risks) with time on study as the underlying time variable and stratified by single year of recruitment and single year of birth. All outcomes of interest were run as separate models. Two main models were made with adjustment for known or potential risk factors for CTS and BTOA.

The first 'minimally-adjusted' model (Model 1) was undertaken adjusting for socioeconomic factors, using deprivation status (as identified by Townsend quintile), geographical region (as identified by 10 geographical regions of the UK) and educational attainment (as identified by highest educational qualification), stratified by year of birth and year of recruitment. The second model (Model 2) fully adjusted for the socioeconomic factors used in model one, plus general and reproductive covariates identified as potential confounders. General covariates used for adjustment were: smoking (categorised as never, past, current); alcohol intake (none, <6units, 6-14, 15+ units/week); strenuous exercise (rare/never, >once per week); Body Mass Index (BMI <25, 25-29.9, 30-34.9, 35+kg/m^2) (and for CTS only, also height (<155cm, 155-159.9, 160-164.9, 165-169.9, >170cm)).[312] Reproductive covariates used were: menarche (<11year, 12, 13, 14, 15+), number of full term pregnancies (in parous women; 0/1/2/3/4+), age at first birth (in parous women; <24 years, 24+ years old), breastfeeding (in parous women; ever/never), OCP use (never/ever,) HRT use

(never/past/current), age at menopause (<46, 46-48, 49-51, 52-53, 54+) and history of bilateral oophorectomy (ever/never). Incremental models were run for each adjustment factor additional to the minimally-adjusted model, to determine the impact of adjustment for each factor upon disease incidence. The category containing the median value for each variable was used as the reference category within each model.

7.4 Results

Analyses included 951 439 post-menopausal women, with a mean age of 58 years (Figure 7.1). When grouped by exposure of interest, the mean follow up time of over 17 years was similar between groups, with those undergoing bilateral oophorectomy being slightly younger at recruitment (Table 7.1). Those women who had their first child at a younger age had a higher level of deprivation and lower level of educational attainment compared to women who had children later in life. Women who had an earlier menopause, did not breast feed and had children earlier have a higher proportion of current smokers and lower engagement with regular strenuous exercise at recruitment. OCP use was lowest in nulliparous women; HRT use is higher at recruitment in those who have undergone bilateral oophorectomy. BMI, height, alcohol intake, prevalence of diabetes appeared similar between groups.

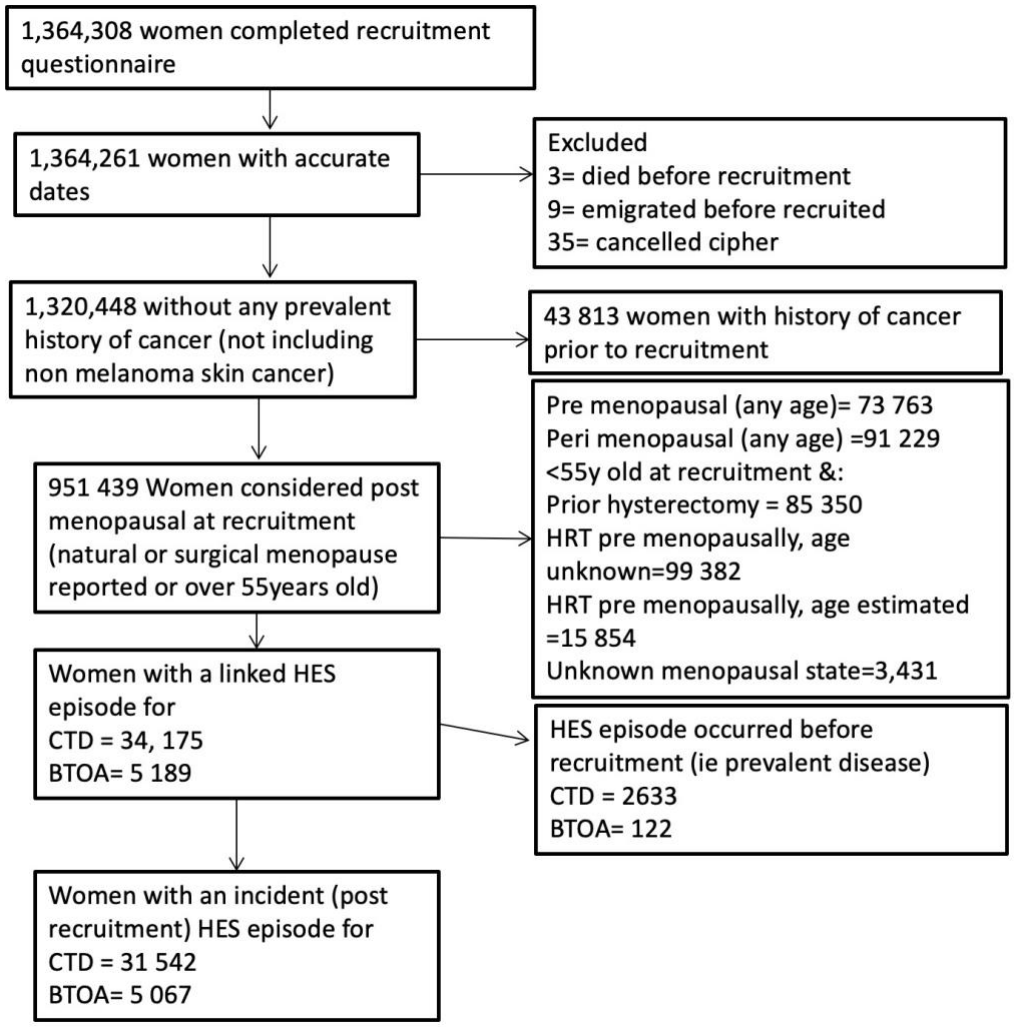


Figure 7.1. Flow Chart of Data management

Characteristics of women at recruitment	**Age at menarche**		**Parity**		**Age at first birth**		**Breastfeeding History if parous**		**Bilateral oophorectomy**		**Age at menopause**	
	<13 years	**13 and over**	**Nullip**	**Parous**	**<24 years**	**24 and over**	**No**	**Yes**	**No**	**Yes**	**<48**	**48 and over**
N	344,345	607,094	105,450	842,153	426,001	525,438	204,561	462,465	646,751	85,202	320,600	630,839
Mean Age at recruitment, years (SD)	57.6 (4.4)	58.1 (4.5)	57.8 (4.8)	57.9 (4.4)	57.7 (4.3)	58.1 (4.6)	57.1 (4.3)	58.4 (4.5)	57.8 (4.7)	56.1 (4.9)	57.7 (4.7)	58.1 (4.4)
Deprivation: least deprived quintile, %	19.9	19.4	20.0	19.5	15.6	22.8	18.7	20.6	19.5	19.7	18.1	20.3
Education: no qualifications, %[a]	39.6	43.7	33.2	43.3	52.7	33.8	48.7	37.2	42.7	41.8	45.3	40.7
Smoking: Current,%	18.8	19.1	16.2	19.3	23.7	15.1	22.4	16.5	19.5	19.3	23.8	16.5
Body mass index: mean (SD), kg/m2	27.0 (4.9)	25.8 (4.4)	25.8 (4.8)	26.3 (4.6)	26.7 (4.8)	25.9 (4.5)	26.5 (4.8)	26.2 (4.5)	26.2 (4.7)	26.7 (4.7)	26.3 (4.7)	26.2 (4.6)
Height: mean (SD), cm	161.4 (6.5)	162.3 (6.6)	162.6 (6.9)	161.9 (6.6)	161.4 (6.5)	162.4 (6.7)	161.4 (6.5)	162.1 (6.5)	161.9 (6.6)	162.0 (6.7)	161.8 (6.7)	162.0 (6.6)
Units of alcohol per week, mean (SD)	3.8 (5.1)	3.9 (5.1)	4.3 (5.7)	3.8 (5.0)	3.6 (5.0)	4.0 (5.2)	3.6 (4.9)	4.0 (5.1)	3.8 (5.1)	3.7 (5.0)	3.7 (5.1)	3.9 (5.2)
Strenuous exercise Rarely/never %[b]	47.5	48.5	47.3	48.3	51.4	45.5	54.0	44.9	48.2	47.9	50.7	46.8
Oral contraceptive use, % ever:	52.8	52.0	37.6	54.2	56.6	48.8	54.7	55.6	51.4	55.6	53.5	51.7
HT use, % never	50.0	50.4	54.5	49.7	47.0	52.4	50.0	49.0	64.6	15.5	45.4	52.7
Past Medical History Diabetes Mellitus[c]	3.7	2.8	3.1	3.1	3.4	2.9	3.5	2.7	3.1	3.2	3.4	3.0
Mean years of follow up per woman (SD)	17.8 (3.6)	17.8 (3.6)	17.6 (3.9)	17.8 (3.6)	17.7 (3.7)	17.8 (3.6)	17.6 (3.5)	17.8 (3.4)	17.8 (3.6)	17.9 (3.4)	17.6 (3.8)	17.9 (3.5)

All characteristics are reported from recruitment questionnaire unless otherwise stated.
a) Left at school leaving age with no qualifications
b) Strenuous exercise refers to physical activity that causes sweating or a fast heart rate
c) Self-reported disease or history of hospital admission at baseline

Table 7.1. Study characteristics of included women

During follow-up, 31 542 CTD cases and 5067 cases of BTOA were identified. The incidence of CTD was 1.90 per 1000 person years (95%CI 1.88-1.92), with a mean age at diagnosis of 68.1 (SD7.50). For BTOA incidence was 3.00 per 10,000 person years (95%CI 2.92-3.01),with a mean age at diagnosis of 69.0 (SD6.18)

The results of the minimally adjusted model for age, region, deprivation and education (model 1) and the final model (model 2) adjusted for all general and reproductive covariates are given in Table 7.2. Incremental models were used to identify the impact of each adjustment variable (Appendix G tables 3-14).

7.4.1 Menarche and childbearing

In the fully adjusted model, early menarche was associated with a higher risk of developing both conditions (CTS RR 1.14, 95% confidence interval 1.10-1.18 for menarche <11years versus median category 13 years; BTOA RR 1.35 (1.21-1.52); absolute values are given in table 7.2). Interestingly, late menarche also increased the risk of BTOA but not of CTS (BTOA, final model, RR 1.21 (1.07-1.36) for menarche >15 years).

When compared to parous women, nulliparous women appeared to have no difference in disease incidence in the fully adjusted model for CTS, but borderline reduced risk of BTOA was seen. Among parous women, there was in the minimally adjusted model a gradual increase in risk of both CTS and BTOA with increasing number of full term pregnancies. This increased risk remained, albeit attenuated, when adjusted in the full model (4+ pregnancies versus 2 pregnancies: CTS RR 1.16 (1.12-1.20); BTOA RR 1.11 (0.98-1.25). Similarly, an early age at first birth (<20 years versus 20-29 years) was associated with increased risk of CTS,

with a similar trend for BTOA that did not maintain significance on full adjustment. Among parous women, those who did not breastfeed had a small reduction in incidence of both CTS (RR compared with parous women with history of breastfeeding, 0.93 (0.90-0.96) and BTOA (RR 0.95 (0.86-1.05)).

Table 7.2: Cox Proportional Hazard models for CTD and BTOA, both models

		CTS						BTOA					
	Total ppn	**Total N of cases**	**Model 1* (age, region, deprivation, education)**			**Model 2** (all general and reproductive factors+ height)**		**Total N of cases**	**Model 1* (age, region, deprivation, education)**			**Model 2** (all general and reproductive factors)**	
		31542	**Adj HR**	**95% CI**		**Adj HR**	**95%CI**		**5067**	**Adj HR**	**95% CI**		**Adj HR**	**95% CI**	
Age at Menarche															
<11y	181 978	7284	**1.27**	1.23	1.31	**1.14**	1.10	1.18	1195	**1.37**	1.26	1.49	**1.35**	1.21	1.51
12	162 367	5305	**1.04**	1.00	1.07	**1.00**	0.97	1.04	845	**1.11**	1.01	1.21	**1.19**	1.05	1.33
13	224 646	7161	**1.00**			**1.00**			1057	**1.00**			**1.00**		
14	195 816	5925	**0.94**	0.90	0.97	**0.95**	0.92	0.98	953	**1.04**	0.95	1.13	**1.03**	0.92	1.16
15+	167 529	5202	**0.95**	0.92	0.99	**0.98**	0.94	1.01	889	**1.14**	1.04	1.24	**1.21**	1.07	1.36
Parity Y/N															
Nulliparous	105 450	3181	**0.93**	0.90	0.97	**0.99**	0.95	1.03	440	**0.80**	0.72	0.88	**0.88**	0.79	0.97
Parous	842 153	28230	**1.00**			1.00			4602	**1.00**			**1.00**		
Number of full term pregnancies (in parous women)															
1	119 036	3497	**0.93**	0.90	0.97	**0.93**	0.90	0.97	559	**0.93**	0.84	1.02	**0.91**	0.81	1.03
2	387 466	12343	**1.00**			**1.00**			2004	**1.00**			**1.00**		
3	212 597	7441	**1.11**	1.07	1.14	**1.07**	1.04	1.10	1274	**1.17**	1.09	1.26	**1.17**	1.07	1.29
4+	123 054	4949	**1.30**	1.26	1.34	**1.16**	1.12	1.20	765	**1.24**	1.14	1.35	**1.11**	0.98	1.25
Age at first birth (in parous women)															
<20 y	102 163	4159	**1.23**	1.19	1.27	**1.10**	1.06	1.14	744	**1.32**	1.22	1.43	**1.09**	0.97	1.22
20-29	636 461	21926	**1.00**			**1.00**			3413	**1.00**			**1.00**		
30+	78 395	2189	**0.86**	0.82	0.90	**0.94**	0.90	0.98	300	**0.73**	0.65	0.83	**0.85**	0.73	0.99

History of Breastfeeding (in parous women)															
No	298 079	9029	**0.91**	0.88	0.94	**0.93**	0.90	0.96	1432	**0.93**	0.86	1.00	**0.95**	0.86	1.05
Yes	462 465	15637	**1.00**			**1.00**			2572	**1.00**			**1.00**		
History of Bilateral oophorectomy (in never users of HRT only total population=478 005)															
Total cases in non HRT users	*12926*								1427						
No Bilateral oophorectomy	464 736	10620	***1.00***			**1.00**			1243	**1.00**			**1.00**		
Bilateral oophorectomy	13 209	496	**1.42**	1.30	1.56	**1.32**	1.21	1.45	68	**1.94**	1.50	2.51	**1.76**	1.35	2.29
Age at natural menopause (never users of HRT only, and without oophorectomy or hysterectomy)															
<46 years	124 096	8866	**1.08**	1.02	1.14	**1.06**	1.01	1.11	1845	**1.17**	1.03	1.34	**1.14**	1.00	1.31
46-48 years	83 081	4790	**1.00**			**1.00**			754	**1.00**			**1.00**		
49-51 years	190 931	7805	**0.98**	0.94	1.03	**0.99**	0.95	1.03	1163	**0.97**	0.86	1.10	**0.98**	0.87	1.11
52-53 years	99 109	4098	**1.01**	0.96	1.07	**1.01**	0.96	1.07	463	**0.85**	0.73	0.99	**0.87**	0.75	1.01
54+ years	68 135	2854	**1.04**	0.98	1.10	**1.03**	0.98	1.09	296	**0.80**	0.68	0.95	**0.81**	0.68	0.97

Ppn= population
All exposures run in individual models.
***Model 1=** cox model adjusted for region, deprivation and education, stratified by year of birth and year of recruitment
****Model 2=** model 1 + general covariates: smoking (never, past, current) alcohol (none, <6units, 6-14, 15+ units/week); strenuous exercise (rare/never, >once per week); BMI (<25, 25-29.9, 30-34.9, 35+kg/m^2) reproductive covariates: age at menarche (<11year, 12, 13, 14, 15+), OCP use (ever/never,) number of full term pregnancies (0/1/2/3/4+), age at first birth (<24 years, 24+ years old), breastfeeding (ever/never), age at menopause (<46, 46-48, 49-51, 52-53, 54+), HT use (never/past/current; adjustment variable for non-menopausal factors only), bilateral oophorectomy (ever/never)
[+]**History of Bilateral oophorectomy and Age at menopause** *(in never users of HRT only; total N=478,005) therefore hrt not used as an adjustment factor in model 2)*

7.4.2 Menopausal factors

The greatest influence of endogenous hormones was seen with menopausal factors.
A history of bilateral oophorectomy was associated with a higher risk of developing both conditions compared to those who had undergone a natural menopause (Tables 7.2 and 7.3, including absolute values), with a particularly large effect on BTOA incidence (in never HRT users, BTOA 1.76 (95% CI 1.35-2.29); for CTS, RR 1.32 (1.21-1.45)). History of bilateral oophorectomy was available for 18,597 women of whom 12,926 were never users of HRT at recruitment. The association of CTS and BTOA with oophorectomy was stronger in never HRT users than in the analysis including all women: Table 7.3).

In never HRT users, early age at natural menopause (<46 years compared to 46-48 years) was associated with a modestly increased risk of CTS (RR 1.06 (1.01-1.11) and of BTOA (RR 1.14 (1.00-1.31). For ages at natural menopause over 48 years there was no trend in risk for CTS, but there appeared to be a trend towards greater reduction in risk of BTOA as age at menopause increased (Table 7.2).

7.4.3 Interaction of age and type of menopause

As mean age at menopause was lower in those undergoing oophorectomy (Table 7.1) it felt pertinent to investigate whether the associated increased risk of CTS and BTOA associated with oophorectomy reflects an interaction with age at menopause. A combined variable of age and type of menopause (oophorectomy or natural) was generated to determine the interaction of the two exposures for those never HRT users, as these women are considered to have a reliable age of menopause recorded unlike their contemporaries who use HRT (Table 7.3 and Figure 7.2; absolute values included in table).[141] Women with a history of

oophorectomy were also much more likely than those with natural menopause to be taking HRT at recruitment (Appendix G Tables 1&2). Bilateral oophorectomy was independently associated with increased disease incidence for both conditions, with the greatest effect when combined with an earlier age at menopause for BTOA (RR 2.05 (1.47-2.85) for those undergoing bilateral oophorectomy before the age of 46 years, versus natural menopause aged 49-51).

Incremental models showed the adjustment factors that generated the most change in the multivariable regression model (Appendix F Tables F.3-F.14). Here, the influence of BMI as an adjustment factor upon CTS incidence is noted in the age at menarche model and parity models (F tables F.3 and F.5), and the influence of HRT use upon the bilateral oophorectomy analysis (F table F.8). For BTOA, history of bilateral oophorectomy appeared to have the clearest impact alongside HRT use as adjustment factors in the multivariable regression (Appendix F tables F.9, F.10, F.12 and F.14).

Table 7.3. Additional analysis of menopausal factors

		CTS						BTOA					
	Total PPN	**Total N of cases**	**Model 1* (age, region, deprivation, education)**			**Model 2** (all general and reproductive factors+ height)**			**Total N of cases**	**Model 1* (age, region, deprivation, education)**			**Model 2** (all general and reproductive factors)**		
	951 439		**Adj HR**	**95% CI**		**Adj HR**	**95%CI**			**Adj HR**	**95% CI**		**Adj HR**	**95% CI**	
History of Bilateral oophorectomy (all women)															
No Bilateral oophorectomy	869 147	18597	**1.00**			**1.00**			907	**1.00**			**1.00**		
Bilateral oophorectomy	82 292	3620	**1.48**	1.43	1.53	**1.15**	1.10	1.19	3794	**2.43**	2.24	2.64	**1.58**	1.44	1.74
History of Bilateral oophorectomy (in never users of HRT only; total N=478,005)- therefore hrt not used as an adjustment factor in model 2															
Total cases in non HRT users	478 005	*12926*							1876						
No Bilateral oophorectomy	464 736	10620	***1.00***			**1.00**			1243	**1.00**			**1.00**		
Bilateral oophorectomy	13 209	496	**1.42**	1.30	1.56	**1.32**	1.21	1.45	68	**1.94**	1.50	2.51	**1.76**	1.35	2.29
Age at menopause and type of menopause as a combined variable (in never HRT users only) *therefore hrt not used as an adjustment factor in model 2*															
Total number of all cases in never HRT users:	478 005	*12926*							1427						
<46y & Natural menopause	64 818	1465	**1.05**	0.99	1.12	**1.02**	0.96	1.09	184	**1.02**	0.85	1.23	**0.98**	0.82	1.18
<46y & Bilateral oophorectomy	7 071	256	**1.62**	1.42	1.85	**1.47**	1.29	1.68	41	**2.20**	1.59	3.06	**2.05**	1.47	2.85
46-48y & Natural menopause	70 856	1483	**0.97**	0.91	1.03	**0.96**	0.90	1.03	181	**0.89**	0.74	1.07	**0.89**	0.74	1.07
46-48y & Bilateral oophorectomy	2 088	72	**1.43**	1.12	1.82	**1.30**	1.02	1.66	10	**1.61**	0.83	3.12	**1.52**	0.78	2.96
49-51y &Natural menopause	138 174	3015	**1.00**			**1.00**			386	**1.00**			**1.00**		
49-51y & Bilateral oophorectomy	2 132	63	**1.28**	0.99	1.65	**1.21**	0.94	1.56	9	**1.64**	0.85	3.18	**1.60**	0.83	3.11
52-53y & Natural menopause	75 669	1773	**1.05**	0.99	1.12	**1.04**	0.98	1.11	172	**0.82**	0.68	0.98	**0.83**	0.69	1.00
52-53y & Bilateral oophorectomy	789	18	**0.99**	0.62	1.58	**0.93**	0.59	1.48	2	**0.93**	0.23	3.74	**0.91**	0.23	3.66
54+ y & Natural menopause	56 482	1417	**1.09**	1.02	1.17	**1.06**	0.99	1.13	132	**0.83**	0.68	1.02	**0.82**	0.67	1.02
54+y & Bilateral oophorectomy	643	19	**1.34**	0.85	2.11	**1.25**	0.79	1.96	0	**0.00**	0.00		**0.00**	0.00	
PPN=population															

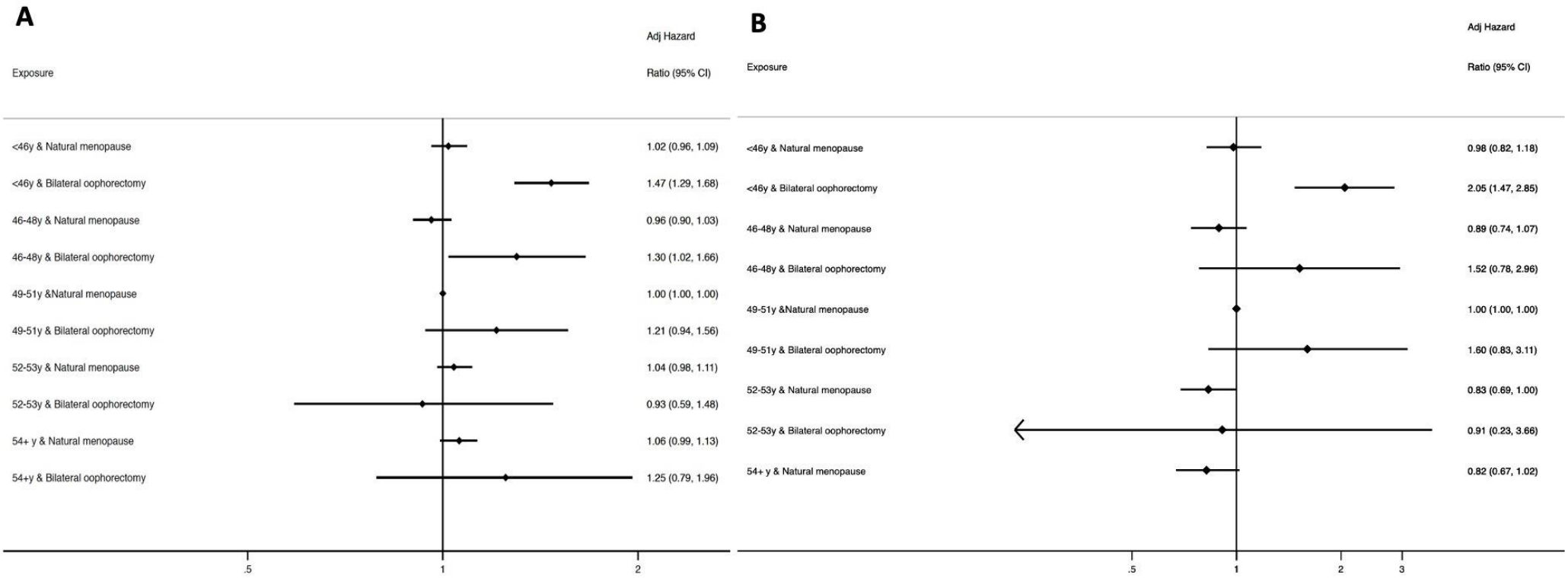


Figure 7.2. Interaction of age and type of menopause, never HRT users. A= incident surgical CTS; B = incident surgical BTOA. See table 7.3 for absolute values

7.5 Discussion

7.5.1 Key findings

Before this study, investigation of endogenous hormonal factors was based in small case series and cohort studies with short term follow up. This study is able to tease apart the impacts of menarche, pregnancy, lactation, natural and surgically induced menopause, analyses which are very limited in the current evidence base.

For both CTS and BTOA our results suggest that early age at menarche, higher parity and early age at first birth are associated with increased incident post-menopausal disease, and both nulliparity and (in parous women) not breastfeeding appear to be protective.

Early age at natural menopause was associated with increased risk of CTS and of BTOA; and a history of bilateral oophorectomy was independently associated with substantially increased risk, with a relative risk of 2-fold for BTOA in women who had undergone oophorectomy under the age of 46 years in never HRT users. It may be pertinent for women undergoing bilateral oophorectomy to be counselled for their increased risk of hand conditions.

Overall, the direction of association was similar for both CTS and BTOA. On occasions this did not appear to reach significance for BTOA, but this is likely to reflect the lower incidence of BTOA outcomes and relative lack of power in these analyses.

Methodologically, this study identified that there is huge strength in prospective, well curated data in adding valuable of collecting lifestyle factors and difficult variables to identify in routine healthcare data to epidemiological analysis. The combination of datasets has enabled conclusions to be drawn that may not have been possible in routine data alone. Repurposing a cohort study designed to investigate pathologies other than orthopaedic conditions is limited by linkage to other data sources identify the orthopaedic outcomes, but the risk of misclassification can be achieved with good validation studies. Despite these strengths, there remains many confounders not explored in this study. This is especially due to time varying confounding within a study spanning 2 decades due to potential trends and changes in healthcare policy and treatment guidance during the study period. This requires a further layer of epidemiological expertise in order to unpack and represents the future work with MWS.

7.5.2 Strengths and Limitations

This large prospective cohort study of nearly one million women post-menopausal women is able to adjust for confounders such as education level, social deprivation, BMI, smoking, alcohol and exercise levels that are often poorly recorded. It also links to national hospital data and death registration to identify validated outcomes, with virtually complete follow-up (<2% lost to follow-up by 2019).

This study uses validated outcomes identified from national hospital admission data, with the benefit of a long follow up. The prospective cohort design enables rich phenotypic information to supplement data found in routinely collected sources, and enables

adjustment for many potential confounders that are difficult to investigate in other populations. It has been difficult to tease apart the heavily related factors of age, age at menopause, the use of HRT, and type of menopause in other studies, and MWS is uniquely positioned in order to do this. A history of oophorectomy was supported by HES recorded procedures in addition to self-reported cases and was isolated from hysterectomy without oophorectomy.

The ability to identify age at menarche and menopause, in addition to a complete birth and breast feeding history, enables investigation of these endogenous factors, which are not fully recorded in routine NHS databases. Appreciating the social and cultural interactions that may influence these factors with the importance of educational and sociodemographic information including smoking, alcohol, and exercise also enables this study to add to the literature.

One must also appreciate potential limitations of this study. The study population was recruited from women who attended screening for breast cancer and will represent a population more readily engaging with healthcare services who are able to provide written consent to the study. The population is predominantly Caucasian, and the influence of ethnicity was not studied in these analyses. Even in such a large study with long follow-up, numbers of women in some analyses were small, especially for BTOA, and for some exposures where RRs were similar, the results for CTS were conventionally statistically significant while those for BTOA were not. This in itself does not provide evidence for a real difference in risk profile between the two outcomes but lack of power does limit some interpretations. The population had a median age of 57 at recruitment, and one must

consider the potential for recall bias of reproductive factors. Variables such as oral contraceptive use and breastfeeding history were considered as binary high-level variables only. One also wonders if there is a level of ascertainment bias generated through the sudden onset of menopausal symptoms associated with oophorectomy, that may cause women to present to medical services with hand conditions, that women who have a more incremental development of symptoms may assign to an ageing process rather than pathology.

Further work is required to unravel the interaction of HRT with oophorectomy and incident disease. The main results are derived from the specific sub cohort of women who in the 1990s underwent oophorectomy and did not then take HRT. Whilst women with a history of any malignancy are excluded from the final cohort, one wonders if there was a particular reason that these women did not take HRT that leaves residual confounding by indication to skew the results. In the incremental models, HRT appears to have a significant impact upon the multivariable model when it is added. In this analysis women were grouped by ever or never exposure to HRT at baseline, as a binary variable, because of likely changes in HRT use during follow-up, with age and due to the controversies around its potential association with cancer, cardiovascular disease and thromboembolic disease that emerged during the study period of this cohort.[313-316]. Nor, for similar reasons, does it aim to provide direct information on the effects of HRT use as an exposure. Further investigation will need to take changes in HRT use during follow-up into account.

Past medical history was gathered either from self-reported fields within the Million Women Study questionnaire, or from hospital records. For conditions not included within

the questionnaire, there is therefore a risk of under identification of these conditions (such as gout) since they were only searched for linked secondary care data. Similarly, incident outcomes of base of thumb osteoarthritis and carpal tunnel syndrome were identified from hospital records, so the study identifies factors associated with the most clinically severe disease requiring secondary care intervention. This emphasises that future work focussed within primary care would build upon this work to determine the role of endogenous hormonal factors in patients presenting in general practice.

7.5.3 Comparison to other studies

Previous work studying the impact of parity upon CTS has predominantly surrounded CTS incidence in pregnancy rather than in later life. In those studies, increasing parity was associated with CTS incidence in pregnant women, fitting with the trend seen in our study.[225, 231, 232, 234, 235] Similarly, studies investigating breast feeding focussed on the post-partum period, where resolution of peripartum CTS was higher in those not breastfeeding.[54] Cross-sectional work from the Netherlands noted that CTS patients were more likely to have undergone hysterectomy & menopause in previous year compared to healthy controls, but the study was unable to establish role of other menopausal factors in multivariable analysis.[317] Pascual *et al.* compared 53 women who had undergone oophorectomy had a relative risk of 4 for CTS compared to 70 healthy controls.[318] From this perspective, this study's findings appear in line with previous work but also adds to the literature through the ability to adjust for many confounders in a large prospective cohort.

For BTOA, there was little consistent clinical evidence identifying the role of endogenous female hormonal factors in disease incidence prior to this study. This may reflect heterogeneity of study design and OA definitions within hand osteoarthritis, in addition to variability in methods for controlling confounding by age. Cross-sectional work in Tasmania concurred with the results in this study, identifying an increased risk of clinical IPJ OA in women who were parous. However, they also found a reduced risk associated with women who breast fed.[58] Age at menarche, menopause, OCP use, duration, number of children and hysterectomy were not found to be significant in this study, which may be due to its small size and due to being undertaken in one community. Fontana *et al.* found a higher prevalence of previous hysterectomy and greater parity in surgically treated BTOA cases than those of ethnicity and 5 year age category matched controls recruited from trauma patients in the same hospital department.[59] An early retrospective cohort study undertaken by Spector *et al.* within the St Thomas's twin registry found higher rates of BTOA in 162 women who had undergone hysterectomy, but lower rates of IPJ OA even when adjusted for age, obesity, parity and smoking status.[319] In comparison, this study is able to tease out the impact of endogenous menopausal factors by the ability to isolate age, age at menopause, and type of menopause experienced.

7.5.4 Interpretation and Generalisability

Understanding of the factors associated with increased risk of severe disease may alert clinicians to those women who may benefit from an earlier referral to secondary care. For both conditions, increasing parity and earlier age at first birth for parous women, and those women who experienced an earlier menarche may be at greater risk of severe disease. For

BTOA, late menarche may also alert clinicians to the potential of severe disease incidence, and for CTS, early menopause, irrespective of how menopause occurred.

This work also suggests that women undergoing oophorectomy are at increased risk of severe carpal tunnel syndrome and hand osteoarthritis, especially if they undergo the procedure at an early age. It could be considered that women should therefore be counselled at the point of consent for oophorectomy and within follow up for the procedure.

Outside the scope of this thesis, further analysis in MWS investigated the influence of hormonal factors upon digital OA (DOA) and subsequently hand osteoarthritis overall. Similar trends were seen in DOA for an increased risk of incident disease with early and late menarche, oophorectomy and the combined effect of age and type of menopause but was not seen with parity or age at first birth. This may reflect the predominantly non-surgical treatment of DOA and lack of HES recorded outcome in addition to a difference in pathoaetiology.

7.5.5 Future research

This work provides greater insight into the role of fluctuations in endogenous female hormones in the aetiology of carpal tunnel syndrome and base of thumb osteoarthritis benefitting from the prospective collection of socioeconomic and demographic factors. This study included a large population of British women from a wide range of geographical areas and parts of society. The educational and reproductive status of the women included is

reflective of their generation, and the results given here are most relevant to the parous population due to small proportion of nulliparous women included. Due to the representative nature of the population included, the study's results have a greater external validity for a European population.

Extension of this work should investigate the time vary confounding that may be driven by HRT use. Further investigation into duration and recency of HRT use, and censoring use within a determined time from recruitment may be useful in determining the role of HRT in disease development. The natural history of HRT use in the UK over the course of the MWS suggests that never HRT users would be unlikely to become new users of HRT after recruitment, but women who were current users at recruitment may have stopped taking HRT. [313-316] During the life course of MWS, high profile media attention of work drawing associations of HRT use with malignancies may have dramatically changed HRT use within the cohort, and this should be investigated for its influence upon CTS and BTOA incidence.

Future work should focus within the role of endogenous hormonal factors in patients presenting in general practice. This could be undertaken in MWS to enable comparison between secondary and primary care diagnoses for less severe CTS and BTOA, or could be undertaken in another prospective cohort study linked to routine primary care data such as UK Biobank.[320] This may enable greater understanding of the role of female endogenous hormones upon the spectrum of hand disease.

8. Federated Network Analysis: OHDSI

The risk of CTS and BTOA after treatment with endocrine blocking treatments for breast cancer[§]

Contributions: All work in this chapter was designed, conducted and analysed by myself apart from replication of my generated analytical package within collaborator datasets. My analytical code was run the following data sources with thanks to the following collaborators:

Source	Collaborator
AUSOM	Dr Seojeong Shin, Dr Seng Chan You
CUIMC	Dr Thomas Falconer
IQVIA Hospital Chargemaster, IQVIA LPD Belgium, IQVIA Openclaims	Mrs Kristin Kostka
SIDIAP, SIDIAP_H	Dr Edward Burn

Analytical code was based upon OHDSI packages designed by Profs Marc Suchard and George Hripcsak, Drs Patrick Ryan and Martijn Schuemie on behalf of the OHDSI community. Assimilation and aggregation of all data into shiny application was undertaken by myself in addition to the meta-analysis.

8.1 Summary

This chapter is a new user comparative cohort study of Aromatase Inhibitors (AI) versus Tamoxifen (TMX) investigating the association of incident BTOA and CTS in postmenopausal women with breast cancer. It represents a study iteratively designed through an open

[§] Based upon work developed in a study in collaboration with Edward Burn, Kristin Kostka, Joshua Ide, Stephen Fortin, Alan Andryc, Thomas Falconer, Anna Oestropolets, Seng Chan You, Seo Jeong Shin, Jose Posada, Dominic Furniss, George Hripcsak, Patrick Ryan, Marc Suchard, and Dani Prieto-Alhambra

science, collaborative approach, and contains a federated network cohort study undertaken in 8 datasets in 5 countries. The study represents one of the first population level estimation studies led from within the University of Oxford using UK primary care data mapped to a common data model outside of covid research. This chapter discusses the advantages and disadvantages of a federated network approach. It highlights the elements of open science and integration of interactive freely available online aggregated data platforms, and both the strengths and weaknesses of being involved in a potentially disruptive innovation before wide scale adoption.

Up to a 2 fold relative risk of both medical and surgical CTS was seen in all datasets for AI users compared to new users of TMX, with an increase in medical BTOA intention to treat one year analysis in OpenClaims (e.g. <5/ 5267 TMX vs 26 cases/13 154 in AI users, one year intention to treat analysis in CPRD for surgically treated CTS; 211/ 146 667 medical BTOA cases in TMX users versus 1 375/ 630 265 AI users in one year intention to treat analysis, OpenClaims). It appears that both CTS and BTOA are early to develop after new use of AIs, which concurs with prior RCTs.

8.2 Introduction

As the systematic review in chapter 6 discusses, RCTs have shown the value of aromatase inhibitors (AIs) in increasing survivorship and reducing recurrence for post-menopausal women with oestrogen receptor (ER) positive breast cancer. [321-323] The two main forms of AIs in use in clinical practice prevent the androgen conversion to oestrogen, either as a reversible non-steroidal inhibitor (such as anastrozole or letrozole) or irreversible steroidal inhibitor (such as exemestane). [324-326] Tamoxifen remains the treatment of choice for pre-menopausal women.

The advent of AIs has now enabled five-year ER positive breast cancer survival to increase to over 90%, and has led to further research into better understanding adverse events associated with hormonal blockade.[327, 328] Musculoskeletal side effects already proposed surround a deterioration in bone health, with an increased risk of osteoporosis and incident fractures associated with AI use compared to tamoxifen.[329-333] Recent work from collaborator colleagues in Catalonia has identified that fracture risk associated with AI can be attenuated by concurrent use of bisphosphonates. [334] The trials discussed in chapter 6 have found an increased risk of CTS as a secondary outcome associated with AI use, an association also found within a retrospective case series in Tunisia. [215, 216, 301, 335] Steroidal aromatase inhibitors (SAIs) appear to have a stronger association with CTS than non-steroidal aromatase inhibitors (NSAIs), but there has been no direct comparison within RCTs to date.

Arthralgia is also a commonly reported side effect associated with AI use, where symptoms appear to be more prominent in those taking HRT prior to cancer treatment, and in the first year of AI use [220, 328, 336] Whilst commonly reported in the literature, large scale clinical trials have not investigated this potential association with OA further.

The development of arthralgia and CTS following AI use has a biological plausibility. Laboratory studies have shown that generation of oestrogen in cartilage is associated with the presence of aromatase. [337] Animal models have identified degradation of cartilage following oophorectomy noting cartilage degradation after ovariectomy, which has also been documented in women after oophorectomy.[338, 339] Tissue samples from patients with hip osteoarthritis have also shown lower levels of aromatase expression in comparison to those with hip fractures.[340] The pathophysiology of increased CTS associated with AI use is

less well investigated within basic science studies, although MRI identified tenosynovial changes in women taking AIs that may identify a potential mechanism of development.[220]

Earlier studies in this thesis have suggested the value of further investigation in this area. In Chapters 3 and 4, there was a strong association seen with the incidence of intervention for both CTS and BTOA for women around the menopause, suggesting that female hormones may be associated with clinically significant disease development. Similarly, the study of the association between endogenous female hormonal factors and CTD and BTOA intervention in Chapter 7 has suggested a strong link with oophorectomy. In order to explore this association from another perspective, investigating the incidence of CTS and BTOA in women taking AIs appeared to be the next logical step.

Initially planned as a discrete analysis within the UK based primary care dataset Clinical Practice Research Datalink (CPRD), it became clear during the course of developing the study that it may be possible to undertake a federated network analysis with the OHDSI network. This study was therefore designed and developed within OMOP CDM mapped CPRD data, with all analytical code developed in a standardised format. Using the OHDSI network of collaborators, this study has been replicated by four data partners in eight datasets and four countries in order to more robustly externally validate findings from within UK data.

The clinical aim of this study was to determine the risk of incident CTS and BTOA in post menopausal women who are new users of tamoxifen versus new users of aromatase inhibitors. The methodological aim of this study was to determine if it was possible to lead, and replicate an OMOP CDM designed surgical study within the OHDSI network and undertake a federated network analysis. The secondary aims were to determine the risk of

incident CTS and BTOA when comparing NSAIs and SAIs and to determine the potential impact of bisphosphonate use upon disease incidence for BTOA.

8.3 Methods

This study was undertaken within the OHDSI and EHDEN network of collaborators using data sources mapped to the OMOP CDM. This network, and the methodology supporting the use of the OMOP CDM are described in chapter 2. Collaborators were invited to participate in the study, with the aim that all partners would participate in running cohort diagnostics in their data source. The iterative nature of designing cohort definitions within the process of cohort diagnostics would ensure that the study would best consider and suit the heterogeneous data sources involved.

The study was designed and led using the ATLAS™ tool OMOP mapped CPRD, with the development of standardised analytical packages in R that could then be shared between collaborators.[341] All analysis was first run in CPRD based within an R Studio environment embedded within an AWS Redshift server to ensure that package was fit for purpose prior to sharing within an open-source web page in GitHub.[342]

8.3.1 Cohort Diagnostics

The Cohort Diagnostics package was used within an iterative process to design the study.[148] Firstly, definitions for exposures and outcomes were generated through identifying appropriate the source codes to generate a concept set expression. This was linked to the standard vocabulary to ensure that the concept set generated would identify observations

in heterogenous data sources. Concept sets were then developed into exposure and outcome cohort definitions through addition of inclusion criteria.

This work predominantly focused upon generating surgical outcome phenotypes across the European, US and Korean datasets, and to enable outcomes to be identified in primary and secondary care data, electronic healthcare records (EHRs) and administrative claims data. Once generated, aggregated cohort diagnostics results could be reviewed by all collaborators to lead discussion within the iterative process.[150-152] Cohort diagnostics results generated results that showed difficulty in generating surgical outcome cohorts, particularly in US data sources. In 2015 conversion from ICD9-ICD10 generated a disparate coding for procedures, losing some granularity of anatomic location, for example in OA. Running sensitivity cohorts including ICD source codes in addition to standard concepts enabled improved generation of the surgical outcomes. This built on industry expertise in device epidemiology, where prior studies had begun in 2015 to prevent coding bias in results.

Based upon this knowledge and iterative process, the decision was also made to undertake a sensitivity analysis with the study period:

1. Due to potential influence of bisphosphonates on OA incidence, removing bisphosphonate users from cohort
2. Due to conversion of ICD9-10 in US in 2015 and the impact seen on surgical outcomes in US datasets in cohort diagnostics, further sensitivity analysis beginning in 2015 was undertaken.

8.3.2 PLE package generation

The final PLE analytical package was developed after three iterations of cohort diagnostics. It was designed in the ATLAS™ tool linked to OMOP mapped CPRD and generated into a full working analytic package with up-to-date OHDSI software using the Hydra R tool.[343] This generated a standardised analytical package that could then be run anywhere within the network in data mapped to the OMOP CDM.

8.3.3 Study Design

This study was designed as a comparative cohort study of the risk of CTS and BTOA in new user of AIs with new users of TMX as an active comparator. A new user, active comparator cohort design was chosen to ensure incident disease identification and to capture the whole period following treatment exposure in follow up.[344]

8.3.3.1 Study period

The study period started 01/01/2006 based upon the emergence of AIs into clinical use and ended at the latest available date for all data sources. Sensitivity analysis used a study period beginning 01/01/2015 to determine the potential impact of change in ICD 9-10 conversion in coding practice that occurred at this time in the US upon CTS and BTOA surgical disease incidence.

8.3.3.2 Participants

This study has been replicated by 5 data partners in 8 datasets 5 countries (UK, US, Spain, Korea and Belgium). Full details of the included datasets are given in Chapter 2.5.4 included national primary care datasets, administrative claims datasets and EHRs.

8.3.3.3 Exposures

AI and TMX new user exposure cohorts were generated for the main analysis, with SAI and NSAI sub cohort generated where available for secondary analysis. Index date for joining the exposure cohort was defined as the first date of drug prescription/dispensation.

Cohort inclusion criteria were:

1. History of Breast cancer: Have a diagnosis (condition occurrence) indicating breast cancer any time within the past 365 days or on the same day as the index event (using the validated definition of breast cancer used in the LEGEND study)[345]
2. No history of secondary malignancy
3. Be aged 55 years or over at index event (indication of post-menopausal status)
4. No prior use of the other drug (i.e. no cross over as would be defined in an RCT)
5. Female sex recorded in notes (ensure data quality and that female breast cancer patients are included in the dataset)
6. Have at least 365 days of continuous observation time prior to index event (sufficient prior exposure to ensure incident exposure and incident outcome, and generate a sufficient clinical picture of past medical history upon which to base the propensity score adjustment)

Persistent exposure to a drug was inferred by allowing up to 30-day gaps between dispensing/prescription records. The AI cohort was considered the 'target' cohort in OHDSI nomenclature and the TMX cohort was defined as the 'comparator'.

For the SAI and NSAI subgroups, prior use of the other subgroup counted as an exclusion for the subgroup analysis. For the bisphosphate subgroup analysis, there was an addition criterion of no use of bisphosphates for the year prior to or including the index date of AI or TMX prescription/dispensation.

Each outcome was analysed individually. The combinations of exposure cohorts run in the final analyses were:

- AI versus TMX
- AI (no bisphosphonate users) versus TMX (no bisphosphonate users)
- NSAI versus TMX
- SAI versus TMX
- NSAI versus SAI

8.3.3.5 Outcomes

Four outcome definitions were generated and analysed in individual models:

1. CTS medical definition based upon diagnosis/condition occurrence.
2. CTD surgical definition based upon procedure occurrence.
3. BTOA medical based upon diagnosis/condition occurrence.
4. BTOA surgical definition based upon procedure occurrence.

Patients were only included if they had no prior outcome within the previous 365 days.

Negative control outcomes were generated to assess for unobserved confounding. A list of potential independent candidates not thought to be causally associated with the exposures was generated using a semi-automated method.[346] This is based upon identifying data from the literature, product labels and reports. Candidate outcomes were then manually reviewed by two clinicians to explore the face validity of the outcomes, ensuring that they do not clinically cause, prevent or treat the outcome but also choose items that are likely to be relatively frequent within the datasets. The list of chosen outcomes is given in Appendix G Table G.1.

8.3.3.6 Follow up

End of follow up was defined in three independent analyses, all using index date as the first prescription/dispensing episode.

1. an intention-to-treat (ITT) analysis continuing until the first from the outcome of interest, date of death (where available), loss to follow up or one year after index date.
2. an intention-to-treat analysis continuing until the first from the outcome of interest, date of death (where available), loss to follow up or until five years after index date
3. an on-treatment analysis continuing until discontinuation, switch or combined therapy plus 30 days, outcome of interest, date of death (where available) and loss of follow up.

Patients were required to have at least 1 day of follow-up for inclusion.

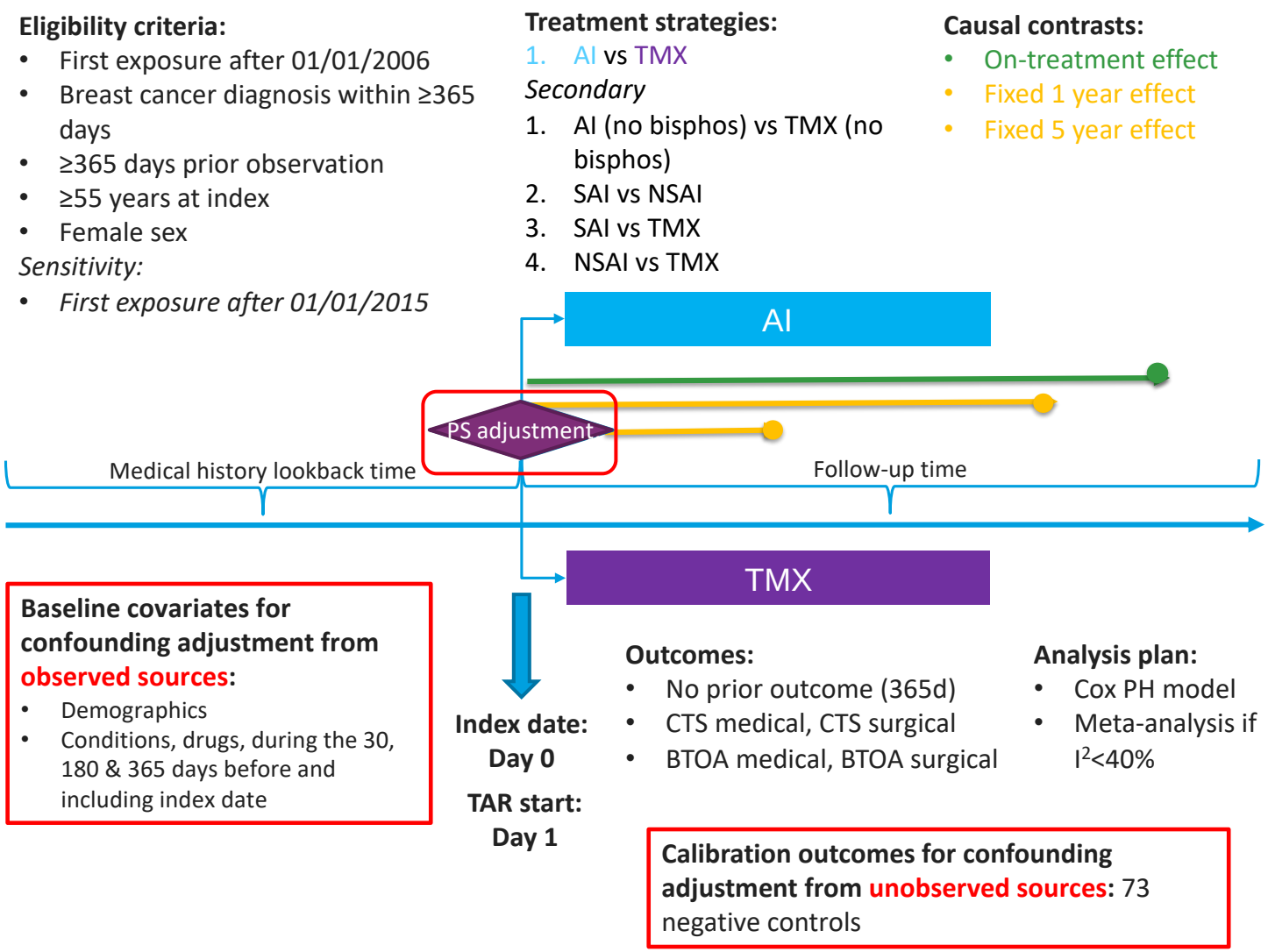


Figure 8.1. Description of study design (acknowledgement to Jamie Weaver for model of infographic)

8.3.4 Statistical Analysis

Overall, 120 unique independent analyses were undertaken in order to include the combinations of 5 pairs of exposures, 4 outcomes, three follow up variations and two study periods.

In order to identify and reduce the potential impact of known confounders, propensity score (PS) adjustment was undertaken using the CohortMethod package.[347, 348] PS adjustment here was designed to predict the probability of exposure given observed baseline characteristics, to address the weakness of treatment ascertainment in observational data. The goal of PS adjustment was to balance target and comparator groups in as many baseline characteristics as possible other than exposure to the new medication, so that should a difference in outcome be found between the two groups, this difference may be attributable with this new drug exposure.

The Cyclops package generated a large-scale data driven PS matching 5:1 (5 target AI cohort:1 comparator TMX).[349] It used baseline covariates based upon the following factors [148]:

Demographics (age, gender, index year, index month, prior observation time)

All conditions occurrence records aggregated to SNOMED clinical finding level during the following lookback windows:

in 365 days prior to and including index date

In 180 days prior to and including index date

in 30 days prior to and including index date

All drug exposure records aggregated to RxNorm ingredient level and ATC classes during the following lookback windows:

in 365 days prior to and including index date

In 180 days prior to and including index date

in 30 days prior to and including index date

persistent exposure that overlaps index date

All condition occurrence records during the following lookback windows:

in 365 days prior to and including index date

In 180 days prior to and including index date

in 30 days prior to and including index date

And excluded covariates known to be associated with treatment e.g., all tamoxifen, AIs, breast cancer and observations associated with dual energy X-ray absorptiometry (DEXA) undertaken routinely at treatment initiation were manually excluded from the PS. Covariates occurring in less than 0.1% of patients in the exposure cohorts were excluded from the PS, and the population was trimmed at <5% and >95% percentiles to maximise equipoise.

This method of PS model generation is a data adaptive, predictive model that reduces overfitting to optimise covariate balance on tens of thousands of candidates. It used a large

scale regularised logistic regression and fitting a Laplace (LASSO) penalty with ten-fold cross-validation to determine the optimal hyperparameter.[350] When testing each covariate for correlation with the target, if high correlation was found consistently found, the PS model was designed to throw an error, to stop fitting and stop the function.

A univariate cox proportional hazard model was used to estimate the risk of outcome, conditioned upon the PS matching and using exposure status as the explanatory variable.

After running the analysis in each data source, aggregated results were shared and placed in the EvidenceExplorer web based shiny application.[153] All study diagnostics were appraised whilst study results were blinded. All data source results were examined individually, and a data source was only included in the final results study diagnostics suggested included data was of sufficient quality. Study diagnostics included assessment of propensity score distribution, covariate balance, systematic error and power (more than 0 events needed for inclusion to generate standard error). Propensity score distribution was inspected visually with qualitative analysis to determine overlap of two groups. Covariate balance was expressed as a standardised mean difference (SMD) before and after PS matching, with a decision made *a priori* that a SMD over 0.1 identified comparator and target cohorts that remained unbalanced despite PS matching and would not pass diagnostic criteria for inclusion in the final results.[351] Systematic error was assessed using negative control outcomes to identify residual unobserved confounding. It was assessed by the power (how many negative control outcomes are detected in the dataset), and then what proportion of the effect estimated contain 1. Of those effect estimates that were outside the null distribution, the direction of skew within the effect estimates was explored to consider how this may impact the results for the outcomes of interest. After determining which datasets

would be included in the final analysis, a meta-analysis was undertaken using a random effects model. The measure of heterogeneity for inclusion in the meta-analysis was set in the protocol, with an I^2 value of <0.4.[352]

8.3.4.1 Sample size

All patients in each data source who met criteria for inclusion were included, without an *a priori* sample size calculation. A minimum detectable relative risk (MDRR) was generated for each individual target-comparator-outcome analysis. This gave the opportunity for data sources that may not have sufficient power in isolation to contribute to a meta-analysis should their study diagnostics show the results meet *a priori* criteria.

All analytic code was made publicly available at https://github.com/ohdsi-studies/MusculoskeletalAEsAfterAIs prior to unblinding results.

8.4 Results

8.4.1 Study Diagnostics

The final PLE study was run in 8 datasets. 1 data source, Ajou University EHR failed to run the full study package due to a high correlation error generated when undertaking PS matching (Table 8.1). 3 data sources did not pass diagnostic testing for containing sufficient power, and sufficiently controlled risk of observed and unobserved confounding despite PS matching. All results were appraised in EvidenceExplorer prior to unblinding (https://jenniferlane.shinyapps.io/EvidenceExplorerMSKAI_working/).

Study diagnostics were appraised for each comparative drug pair, for each outcome, and each analysis plan. The overall summary of study diagnostic results is shown in Table 8.1.

Database	Power?	Propensity Score distribution?	Covariate Balance?	Systematic Error?
CPRD	For all but BTOA surgery	✓	✓	✓
SIDIAP	Medical outcomes only	✓	✓	✓
SIDIAP_H	Medical outcomes only	✗	✗	✓
IQVIA Hospital Charge Master	✓	✓	✓	✓
IQVIA OpenClaims	✓	✓	✓	✓ (high power)
IQVIA LPD Belgium	✗	✓	✗	
Columbia University Irving Medical Centre, NYC, USA	Medical outcomes only	✗	✗	✓
Ajou University, Korea	NA	NA (high correlation during PS generation)	NA	NA

Table 8.1 Study diagnostics results

Results for the main AI vs TMX analysis using the ITT one year follow up design for the CTS condition outcome are given here as an example of the appraisal process. Diagnostics for all other drug comparison pairs, outcomes and study designs available within the EvidenceExplorer application.

An example of good covariate balance, PS distribution and systematic error plots within the shiny app are shown in CPRD (Figures 8.2-8.4) By comparison, those datasets that were not of sufficient quality were LPD Belgium, CUIMC and SIDIAP_H. An examples of poor covariate balance, PS distribution and systematic error indicating residual confounding within these datasets are shown in Figures 8.5 and 8.6.

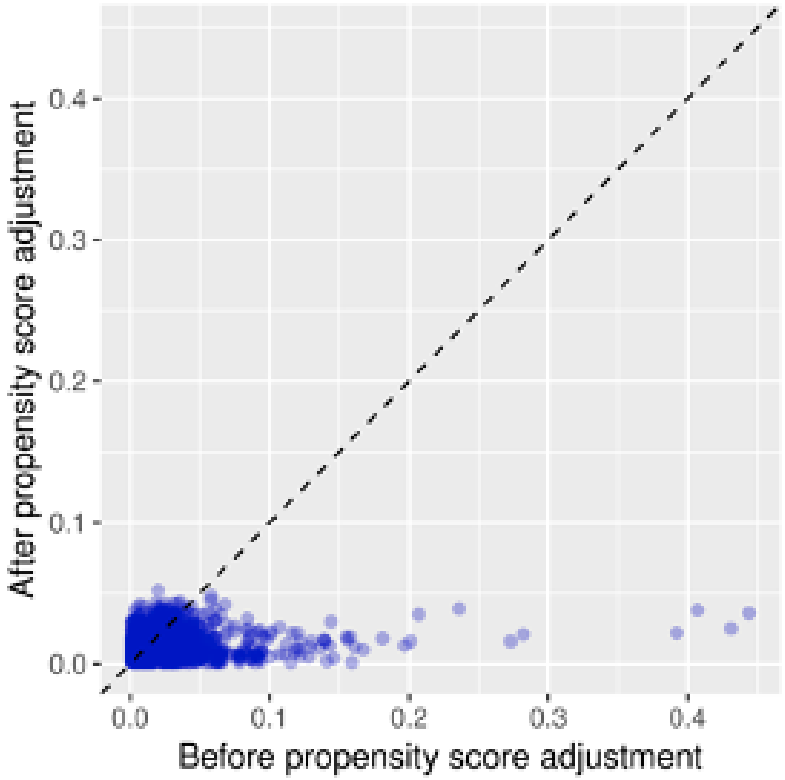


Figure 8.2. Covariate balance for examination of observed confounding, CPRD, ITT one year, AI vs TMX, CTS condition outcome

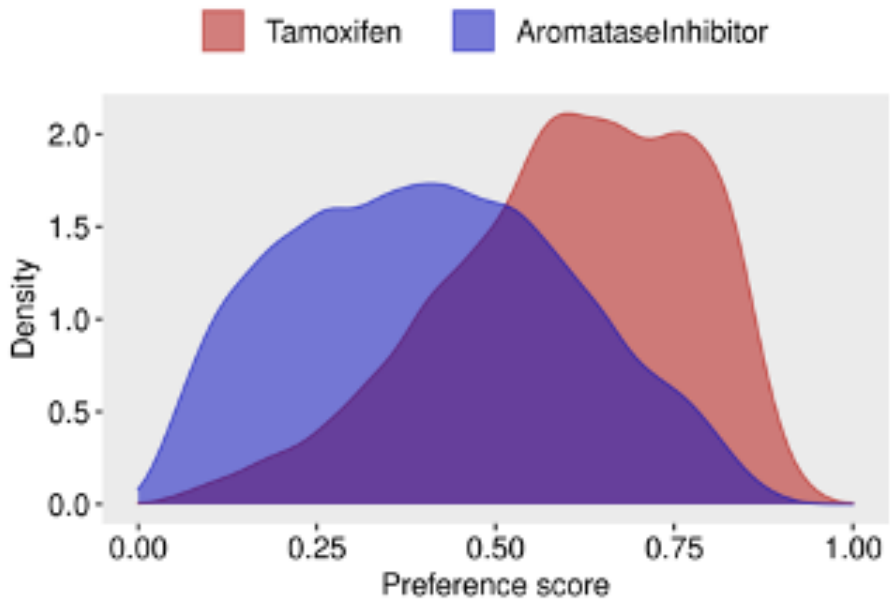


Figure 8.3 PS density plots, CPRD, ITT one year, AI vs TMX, CTS condition outcome

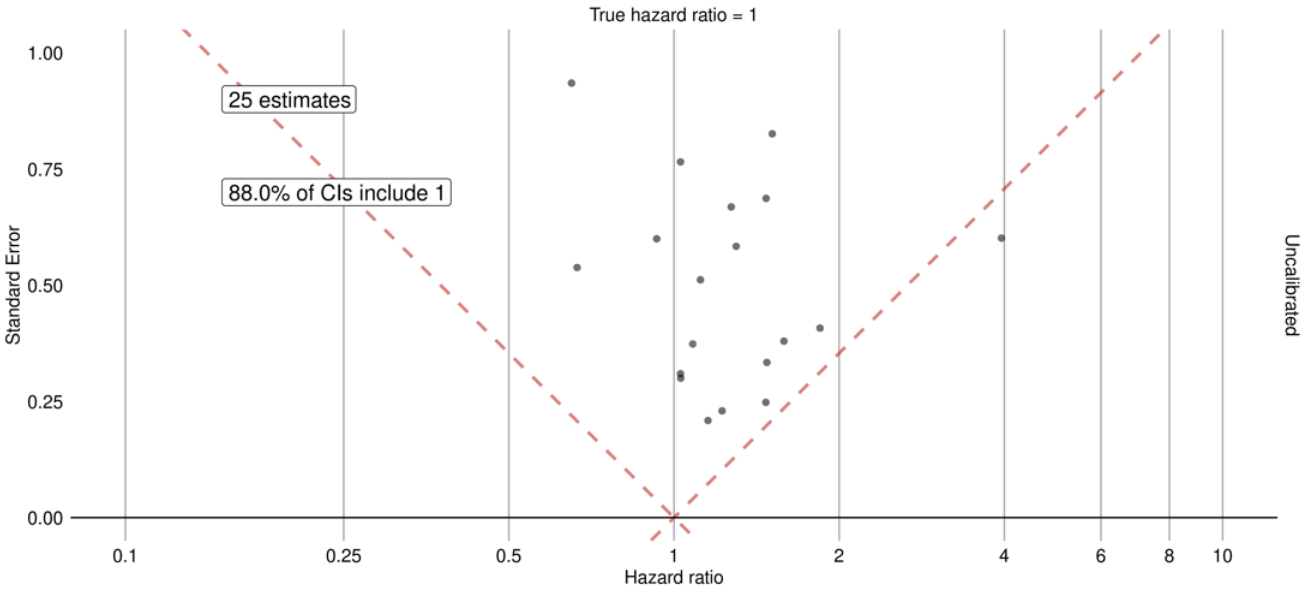


Figure 8.4 Systematic error Negative control outcomes for unobserved confounding CPRD, ITT one year, AI vs TMX, CTS condition outcome.

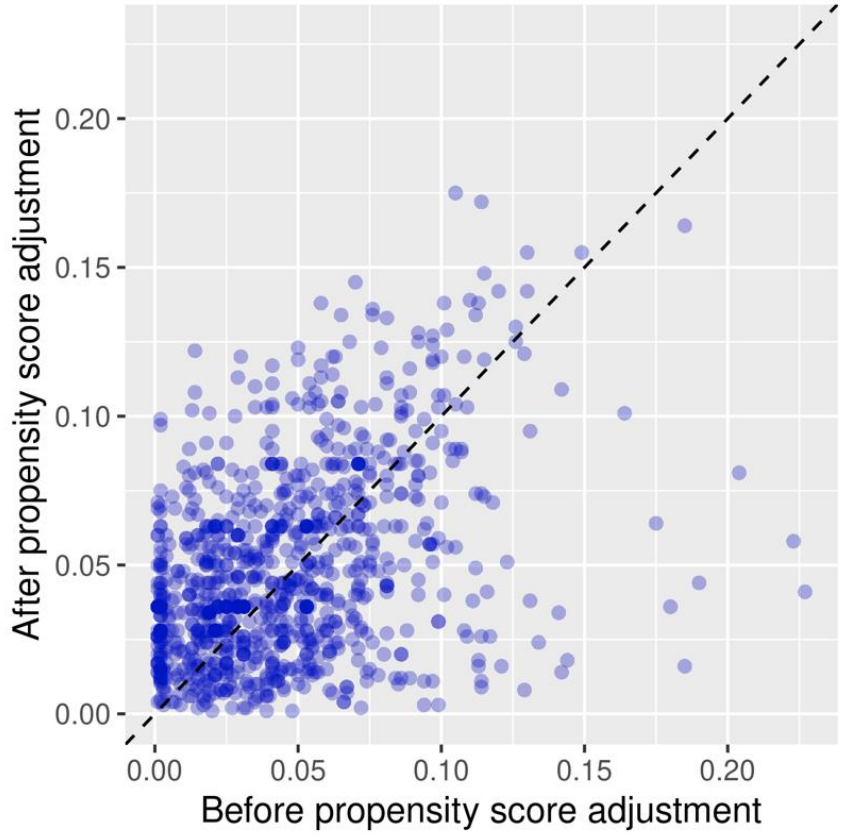


Figure 8.5. Covariate balance, LPD Belgium ITT 1 year follow-up, AI versus TMX, CTS condition outcome.

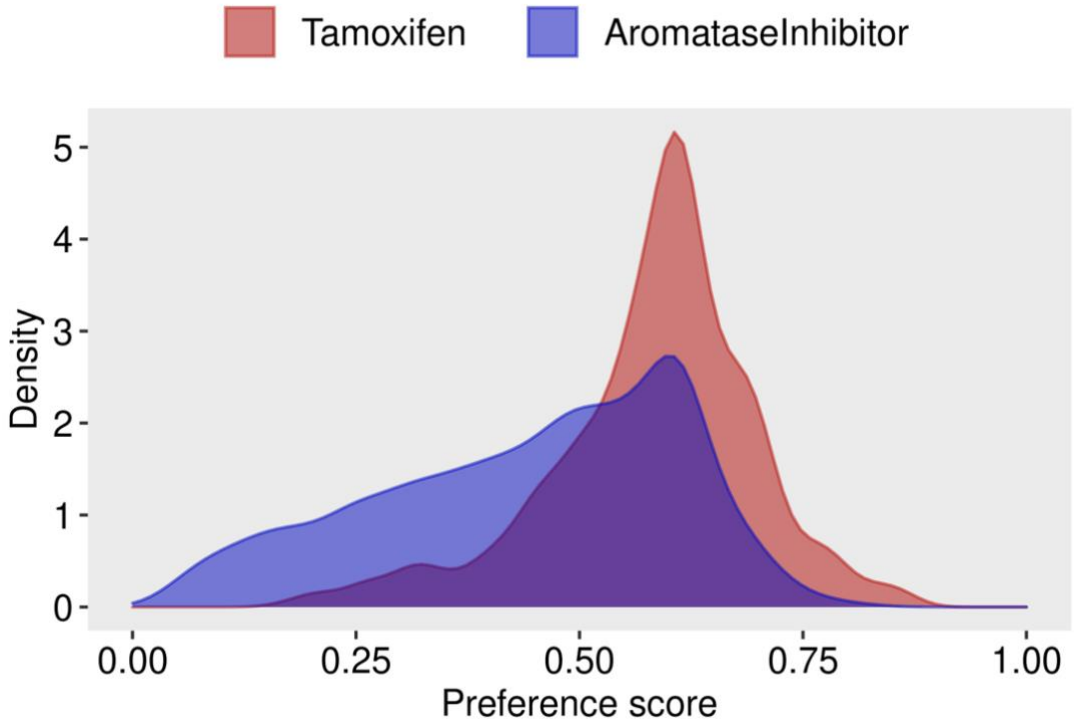


Figure 8.6. Propensity score density plot, CUIMC ITT 1 year follow up, AI versus TMX, CTS condition outcome.

The benefit of the interactive element of the shiny app is the ability to critique data in more depth. For example, one can 'hover' over the data points to identify which covariates within the covariate balance plot remain less balanced.

In depth examination of systematic error noted that LPD Belgium was underpowered, as was SIDIAP_H (Table 8.2). These example figures for the ITT one year follow up analysis show that 1 negative control outcome was identified not to include the null in CPRD and SIDIAP, and both of these outcomes were positively associated with TMX use. Positive skew of variables not including one was also seen in OpenClaims, suggesting that in all three of these populations, women taking TMX may have greater levels of comorbidity than those taking AIs.

Table 8.2 Systematic error analysis for ITT 1 year model, AI vs TMX, CTS condition outcome.

Database	**Systematic error**		
	Power	**%**	**Skew?**
CPRD	25	88	1 outcome not incl null-positive skew
SIDIAP	20	95	1 outcome not incl null-positive skew
SIDIAP_H	15	100	No
IQVIA Hospital Charge Master	35	100	No
IQVIA OpenClaims	64	84.4	Positive skew
IQVIA LPD Belgium	7	100	No
Ajou University, Korea	NA	NA	NA
Columbia University Irving Medical Centre, NYC, USA	18	100	No

8.4.2 Patient characteristics

A more conventional method of appraising the potential for residual confounding of exposure cohorts aside from a covariance balance plot is through reviewing patient characteristics. Table 8.3 gives a traditional table of examples for some pertinent baseline characteristic data before and after the PS matching process for the AI versus TMX medical

CTS analysis. This is given to illustrate the full data available in the EvidenceExplorer to compare the datasets. For any factor of interest one can use the 'raw' button in the 'population characteristics' tab to free text search for any variable that is mapped in the CDM. This is one of benefits of the interactive process within the EvidenceExplorer application, as the reviewer can choose which variables are most interesting to them. A reviewer can also search directly on the PS adjustment plot in the 'covariate balance' tab to graphically appraise the adjustment and 'hovering' over the factors in the plot. Example tables for the other contributing datasets in the main AI vs TMX analysis for the outcome of medically defined CTS are given in Appendix G Tables G.2-G.4.

Table 8.3 Example patient characteristics AI vs TMX ITT one year follow up for medical CTS in CPRD, prior to and after PS adjustment and standardised mean difference.

	Before PS adjustment			**After PS adjustment**		
Characteristic	**TMX**	**AI**	**Std Diff**	**TMX**	**AI**	**Std Diff**
	%	%		%	%	
Age in years	68.367	71.123	-0.282	68.757	68.948	-0.020
Medical History						
Obesity	0.004	0.002	0.028	0.003	0.002	0.01
Osteoarthritis	0.018	0.016	0.011	0.013	0.013	0.003
DM	0.015	0.015	-0.002	0.015	0.015	-0.001
Hypothyroidism	0.006	0.007	-0.008	0.005	0.008	0.006
Rheumatoid arthritis	0.002	0.001	0.007	0.002	0.002	0.007
Gout	0.003	0.005	-0.04	0.003	0.003	0.003
TMX = tamoxifen; AI = Aromatase Inhibitor PS= propensity score Std Diff= standardised mean difference (Note all medical history fields are taken from 'condition era, recorded in the data within-365 to 0 days prior to starting drug of interest as the 'index event')						

8.4.2.1 Attrition of included patients

An example flow chart for patient inclusion for CPRD ITT one year analysis for CTS is given in Figure 8.7, with all other datasets for this group of analyses in SIDIAP, Hospital Charge DataMaster and OpenClaims in Appendix G Figures G.1-G.3, and all others within evidence explorer.

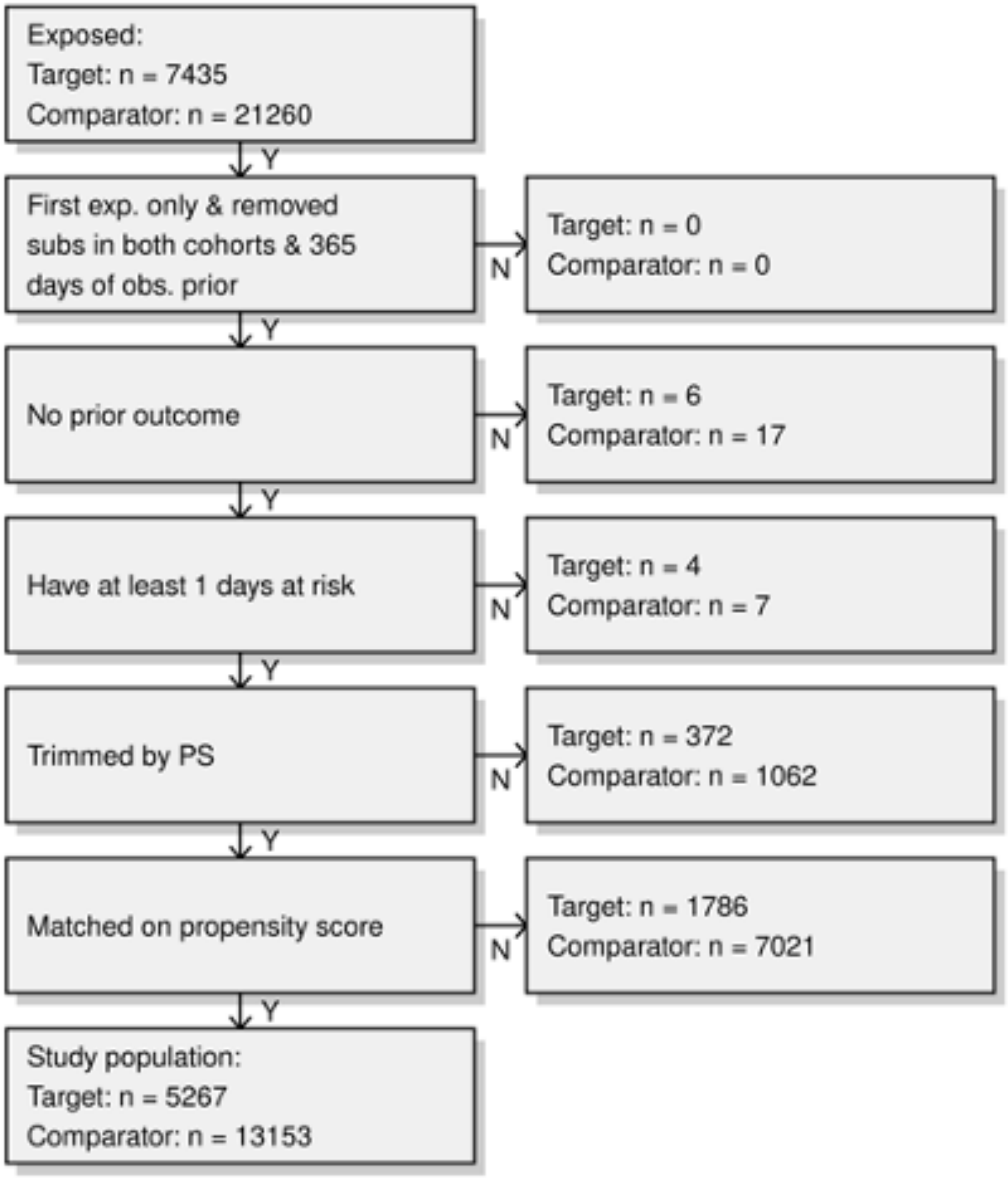


Figure 8.7 CPRD Included patient flow diagram, AI vs TMX, CTS condition outcome, ITT 1 year analysis

8.4 2.2 Patient counts, event counts and, incident rates for CTS and BTOA, Tamoxifen versus Aromatase Inhibitors

The number of patients included in each dataset, for each outcome and analysis plan are given in Table 8.4. This emphasises the relative size of OpenClaims in representing >95% US claims, with CPRD being the next biggest dataset included.

Table 8.4 Patient counts, event counts and incidence rates for medically defined CTS, surgically defined CTS, medically defined BTOA and surgically defined BTOA, all included datasets

	On-Treatment						**ITT 1 year follow up**						**ITT 5 year follow up**					
	TMX user	**AI users**	**TMX events**	**AI events**	**TMX IR**	**AI IR**	**TMX user**	**AI users**	**TMX events**	**AI events**	**TMX IR**	**AI IR**	**TMX user**	**AI users**	**TMX events**	**AI events**	**TMX IR**	**AI IR**
CTS medical diagnosis																		
CPRD	6,585	15,887	128	291	3.72	4.19	5,267	13,153	19	78	3.84	6.41	5,267	13,153	70	218	3.72	5.04
SIDIAP	3,307	11,750	120	358	5.65	5.24	2,647	10,120	9	73	3.50	7.45	2,647	10,124	66	229	6.20	5.86
HCDM	2,259	9,133	21	106	3.68	4.81	1,823	7,634	6	40	4.40	7.14	1,826	7,643	17	82	4.47	5.19
OC	176,076	722,605	6,414	29,374	6.53	7.69	146,314	628,667	828	6,391	5.85	10.54	146,313	628,639	3,725	20,368	6.57	8.55
CTS surgical diagnosis																		
CPRD	6,592	15,907	54	153	1.55	2.18	5,267	13,154	<5	26	<1.01	2.13	5,268	13,153	26	113	1.37	2.60
SIDIAP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HCDM	2,267	9,165	5	32	0.87	1.43	1,826	7,646	<5	12	<3.66	2.13	1,829	7,657	<5	21	<1.30	1.32
OC	176,822	725,853	2,489	12,090	2.48	3.08	146,623	629,996	242	2,338	1.70	3.83	146,620	629,959	1,353	8,305	2.36	3.43
BTOA medical diagnosis																		
CPRD	6,603	15,923	10	7	0.29	0.10	NA	NA	NA	NA	NA	NA	5,272	13,165	<5	5	<0.26	0.11
SIDIAP	3,315	11,775	84	250	3.90	3.61	2,651	10,131	6	37	2.33	3.77	2,650	10,135	46	153	4.30	3.88
HCDM	2,270	9,174	6	21	1.04	0.94	NA	NA	NA	NA	NA	NA	1,831	7,658	<5	16	<1.30	1.00
OC	176,958	726,482	3,190	12,201	3.17	3.09	146,667	630,265	211	1,375	1.48	2.25	146,666	630,228	1,368	6,602	2.38	2.72
BTOA surgical diagnosis																		
CPRD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SIDIAP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HCDM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
OC	177,202	727,573	5	11	0.00	0.00	NA	NA	NA	NA	NA	NA	146,762	630,651	<5	7	<0.01	0.00

IR incidence rate per 1000 person-years
CPRD=clinical practice research datalink; SIDIAP= Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària
HCDM=IQVIA HospitalChargeDataMaster OC=IQVIA OpenClaims

s

All included datasets were able to investigate the association of AI use compared to TMX with medically diagnosed CTS; SIDIAP being based in primary care not contributing to the either CTS or BTOA surgical analyses. Medically diagnosed BTOA was a much rarer incident event, and therefore was only detected in all datasets in the on treatment and ITT five-year analyses; only OpenClaims and SIDIAP powered for the ITT one year follow up analysis. For surgically treated BTOA only OpenClaims was sufficiently powered for analysis.

The incidence of medical CTS was higher in new users of AIs compared to new users of TMX in CPRD, Hospital Charge DataMaster and OpenClaims in all analyses. The increased incidence in AI users was particularly prominent in the intention to treat analyses. SIDIAP noted a two-fold incidence of medical CTS in the one year follow up intention to treat analysis, but a similar incidence of CTS for AI and TMX users in the on treatment and ITT five year follow up.

The rate of incident medical BTOA in the ITT one year follow up was slightly higher in AI users, but this signal was not seen in the ITT 5 year follow up, nor on-treatment analyses where incident medical BTOA appeared to be similar if not slightly higher in new users of TMX. The rate of surgical BTOA appeared similarly rare in both AI and TMX users in Open Claims.

8.4.3 Comparative Risk Associations

8.4.3.1 ITT 1 year

The relative risk of incident medically treated CTS was over 80% higher in women taking AIs (Table 8.5; includes absolute values). A twofold risk of surgically treated CTS was seen in Open Claims but did not reach significance in Hospital Charge DataMaster or CPRD. Analysis for BTOA was only able to be undertaken in two datasets where similar relative risk value for increased risk of incident medical BTOA was seen in Open Claims and SIDIAP but did not reach significance in SIDIAP due to low power.

8.4.3.2 ITT 5 year follow up

If ITT follow up was extended to five years, an attenuated risk of incident CTS was seen compared to the analysis limited to one year (Table 8.6; includes absolute values). An increased risk remained but reduced to approximately 30-50% increased risk in AI users compared to those taking tamoxifen. All four datasets were able to contribute to analyses of incident medical BTOA with the five year follow up. An increased risk of incident medical BTOA was seen in Open Claims but again was attenuated compared to the ITT short term follow up, with no association seen with either drug use in the other three datasets.

8.4.3.3 On Treatment

Similar findings were seen in the on-treatment analyses (Table 8.7; includes absolute values). An increased risk of incident medically treated CTS was seen in CPRD and Open Claims, with no association seen in Hospital Charge DataMaster and SIDIAP. In CPRD and OpenClaims, the relative risk increase was around 23-32% in those women

taking AIs compared to those taking tamoxifen. A higher relative risk was seen for incident surgically treated CTS in CPRD and OpenClaims, with no association seen in Hospital Charge DataMaster. No association was found for incident surgically treated BTOA with either drug.

Table 8.5 ITT 1 year follow up relative risk out CTS and BTOA outcomes, data sources passing study diagnostic thresholds for data quality

	TMX (cases /total)	AI (cases /total)	CPRD		TMX (cases/ total)	AI (cases/ total)	SIDIAP		TMX (cases /total)	AI (cases /total)	HCDM		TMX (cases/ total)	AI (cases/ total)	OpenClaims	
			HR	95% CI			HR	95% CI			HR	95% CI			HR	95% CI
CTS Medical	19/ 5 267	78/ 13 153	1.89	1.15-3.23	9/ 2 647	73/ 10 120	2.38	1.23-5.00	6/ 1 823	40/ 7 634	1.59	0.70-4.17	828/ 146 314	6 391/ 628 667	1.82	1.69-1.96
CTS Surgical	<5/ 5 267	26/ 13 154	2.56	0.95-9.09	NA	NA	NA	NA	<5/ 1 826	12/ 7 646	1.39	0.34-9.09	242/ 146 623	2 338/ 629 996	2.22	1.96-2.56
BTOA Medical	NA	NA	NA	NA	6/ 2 651	37/ 10 131	1.56	0.70-4.17	NA	NA	NA	NA	211/ 146 667	1 375/ 630 265	1.43	1.23-1.64
BTOA surgical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

HR= hazard ratio; 95% CI= 95% confidence interval CPRD=clinical practice research datalink; SIDIAP= Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària; HCDM=IQVIA HospitalChargeDataMaster OC=IQVIA OpenClaims

Table 8.6 ITT 5 year follow up relative risk out CTS and BTOA outcomes, data sources passing study diagnostic thresholds for data quality

	TMX (cases /total)	AI (cases /total)	CPRD		TMX (cases/ total)	AI (cases/ total)	SIDIAP		TMX (cases /total)	AI (cases /total)	HCDM		TMX (cases/ total)	AI (cases/ total)	OpenClaims	
			HR	95% CI			HR	95% CI			HR	95% CI			HR	95% CI
CTS Medical	70/ 5 267	218/ 13 153	1.49	1.12-2.04	66/ 2 647	229/ 10 124	1.04	0.78-1.39	17/ 1 826	82/ 7 643	1.32	0.73-2.50	3 725/ 146 313	20 368/ 628 639	1.33	1.28-1.37
CTS Surgical	26/ 5 268	113/ 13 153	2.22	1.41-3.70	NA	NA	NA	NA	<5/ 1 829	21/ 7 657	0.91	0.24-4.35	1 353/ 146 666	8 305/ 629 959	1.45	1.37-1.54
BTOA Medical	<5/ 5 272	5/ 13 165	0.39	0.05-2.56	46/ 2 650	153/ 10 135	0.97	0.69-1.39	<5/ 1 831	16/ 7 658	1.25	0.34-5.88	1 368/ 146 666	6 602/ 630 228	1.10	1.04-1.18
BTOA surgical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	<5/ 146 762	7/ 630 651	1.92	0.33-33.33

HR= hazard ratio; 95% CI= 95% confidence interval CPRD=clinical practice research datalink; SIDIAP= Sistema d'Informació pel Desenvolupament de

la Investigació a l'Atenció Primària; HCDM=IQVIA HospitalChargeDataMaster OC=IQVIA OpenClaims

Table 8.7 On Treatment follow up relative risk out CTS and BTOA outcomes, data sources passing study diagnostic thresholds for data quality

	TMX (cases /total)	**AI (cases /total)**	**CPRD**		**TMX (cases/ total)**	**AI (cases/ total)**	**SIDIAP**		**TMX (cases/ total)**	**AI (cases /total)**	**HCDM**		**TMX (cases/ total)**	**AI (cases/ total)**	**OpenClaims**	
			HR	**95% CI**			**HR**	**95% CI**			**HR**	**95% CI**			**HR**	**95% CI**
CTS Medical	128/ 6 585	291/ 15 887	1.32	1.03-1.67	120. 3 307	358/ 11 750	1.14	0.90-1.45	21/ 2 259	106/ 9 133	1.11	0.66-1.96	6 414/ 176 076	29 374 / 722 605	1.23	1.19-1.27
CTS Surgical	54/ 6 592	153/ 15 907	1.82	1.23-2.70	NA	NA	NA	NA	5/ 2 267	32/ 9 165	1.09	0.41-3.45	2 489/ 176 822	12 090/ 725 853	1.30	1.23-1.37
BTOA Medical	10/ 6 603	7/ 15 923	0.50	0.10-2.08	84/ 3 315	250/ 11 775	1.18	0.90-1.56	6/ 2 270	21/ 9 174	0.61	0.18-2.44	3 190/ 176 958	12 201/ 726 482	1.01	0.90-1.56
BTOA surgical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5/ 177 202	11/ 727 573	0.43	0.12-1.59

HR= hazard ratio; 95% CI= 95% confidence interval CPRD=clinical practice research datalink; SIDIAP= Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària; HCDM=IQVIA HospitalChargeDataMaster OC=IQVIA OpenClaims

Meta-analyses were undertaken for medically defined and surgically CTS and medically defined BTOA only, as OpenClaims was the only set contributing to the surgically defined BTOA analysis (Figures 8.8-8.10). The relative magnitude of OpenClaims in comparison to CPRD, SIDIAP and Hospital Charge DataMaster is emphasised within the meta-analysis, as the value closely resembles the individual OpenClaims analysis. All three had a heterogeneity <0.4 due to the large proportion of data provided by OpenClaims and quite consistent findings across databases. The forest plots show the difference between the three analytic designs, with a larger association of women taking AIs presenting with incident CTS in the first year after starting the drug (Figures 8.8 and 8.9). This is particularly prominent in the surgical CTS analysis where a two-fold relative risk is seen new users of AI. When undertaking the meta-analysis for medically defined BTOA, the overall impression of the results changes due to the large impact of OpenClaims. Upon first inspection of individual data source results it appears that there is no association seen with incident BTOA, but figure 8.10 shows that there is an increased risk of presentation in the first year of drug use of AIs compared to TMX that is not found with prolonged follow up.

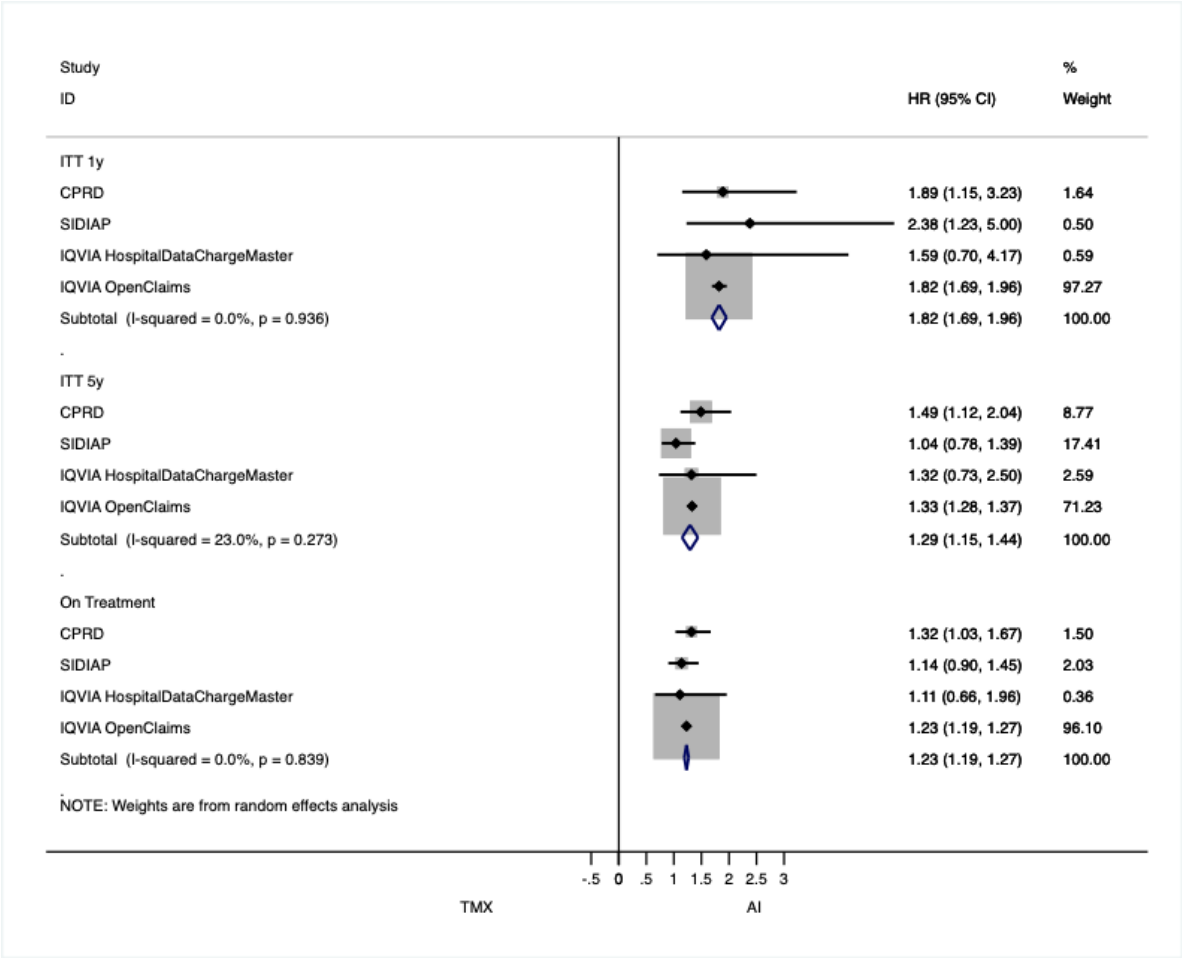


Figure 8.8 Forest plot for AI-TMX drug comparison for CTS medical outcome with meta-analyses. See tables 8.5-8.7 for absolute values

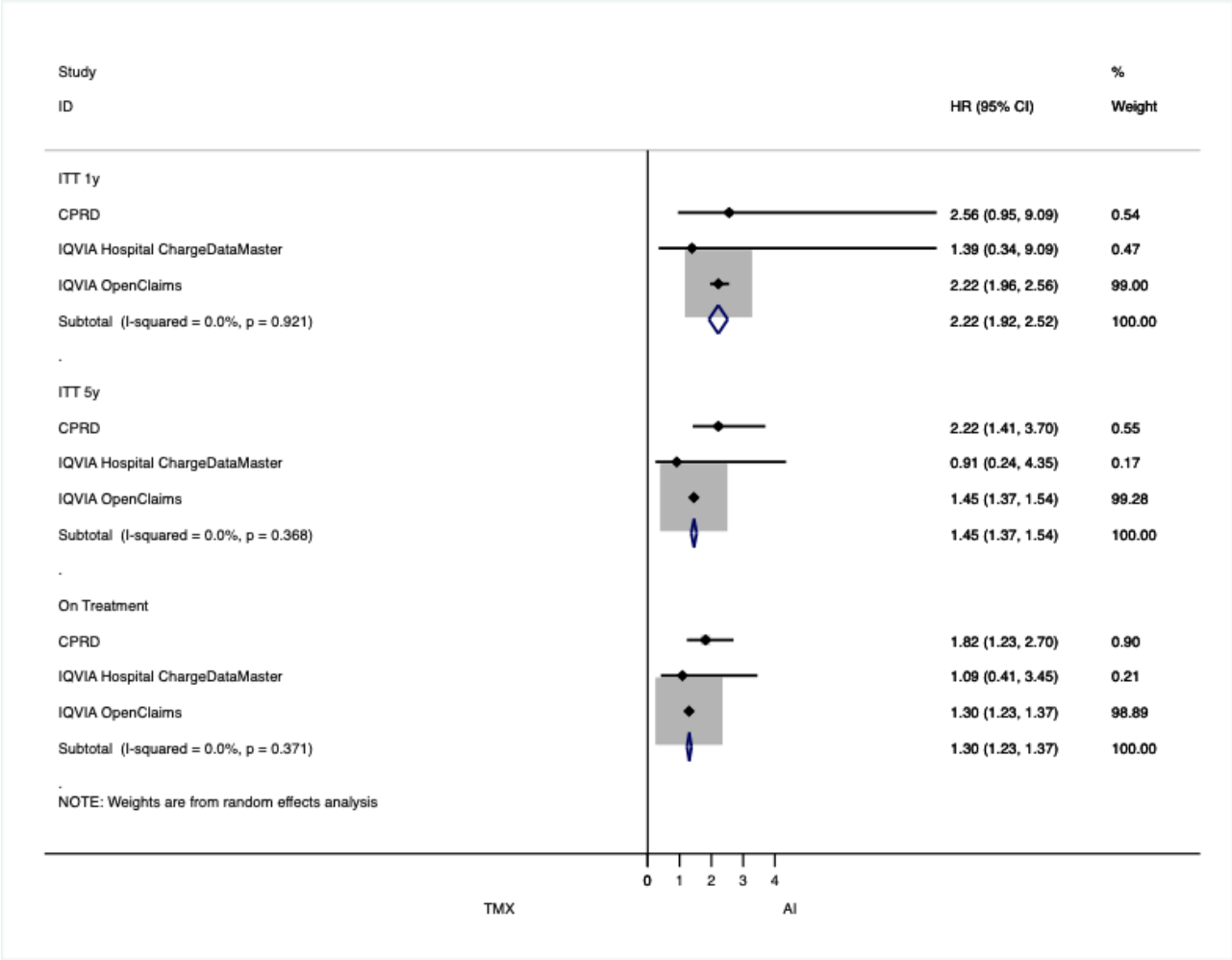


Figure 8.9 Forest plot for AI-TMX drug comparison for CTS surgical outcome with meta-analyses. See tables 8.5-8.7 for absolute values

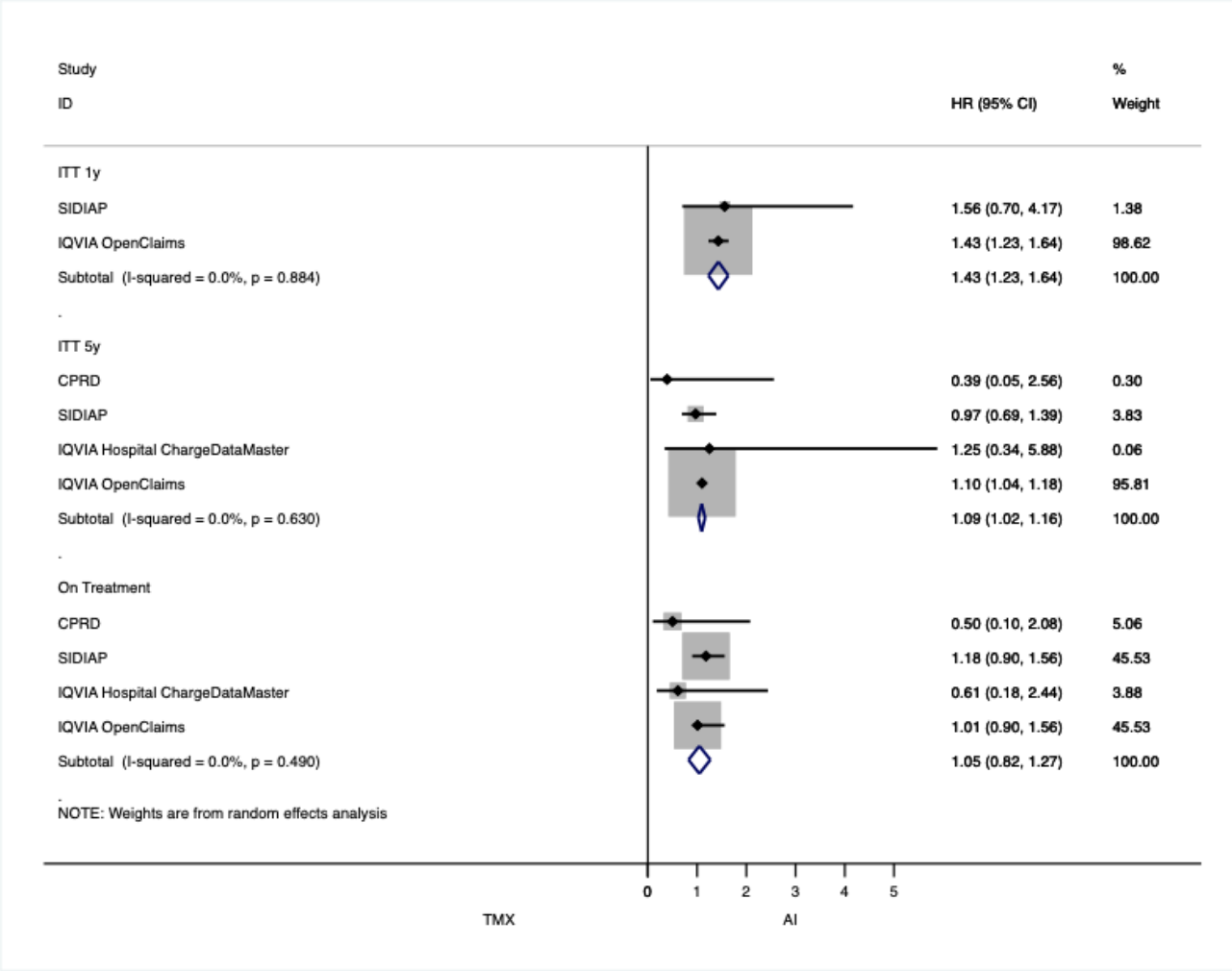
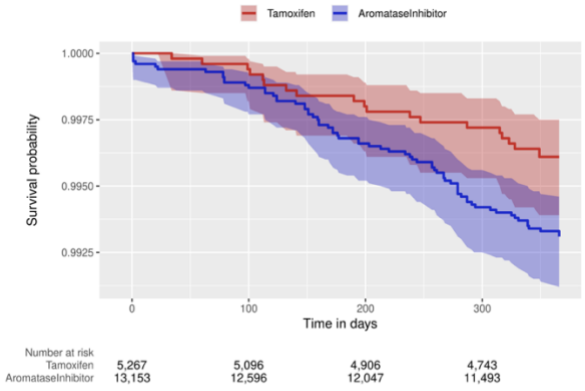


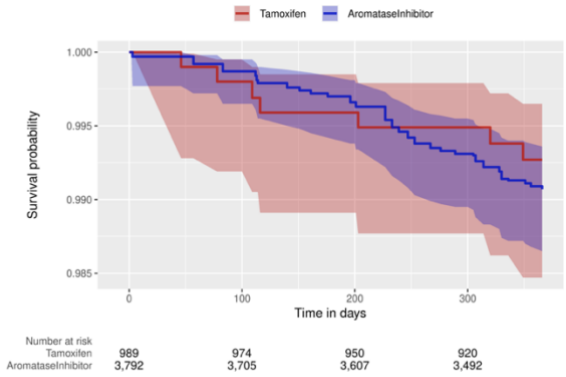
Figure 8.10 Forest plot for AI-TMX drug comparison for BTOA medical outcome with meta-analyses. See tables 8.5-8.7 for absolute values

Kaplan Meier analysis emphasises both the difference and similarities between the included datasets. Examples for the analyses investigating incident medically diagnosed CTS for the three analysis designs are given in Figures 8.11-8.22. The trends are similar between the heterogeneous data sources that represent UK and Catalan primary care and US claims data, but the difference in power and associations that can be drawn from each analysis is clearly identifiable in the plots. The difference between the ITT one year, ITT five year and On treatment analyses is also well represented, with a larger apparent difference between the two exposure groups seen in the shorter ITT analysis. All Kaplan Meier plots for the other three outcomes in the main study are given in Appendix G Figures G.4-G.24, with the plots for the sensitivity analyses present within the shiny application.

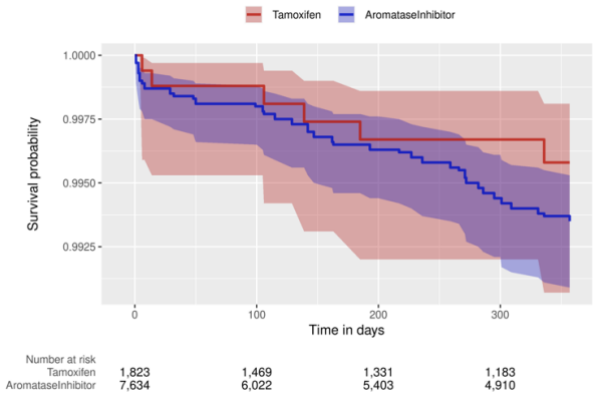
8.4.3.4 Medical CTS- ITT 1 year follow up



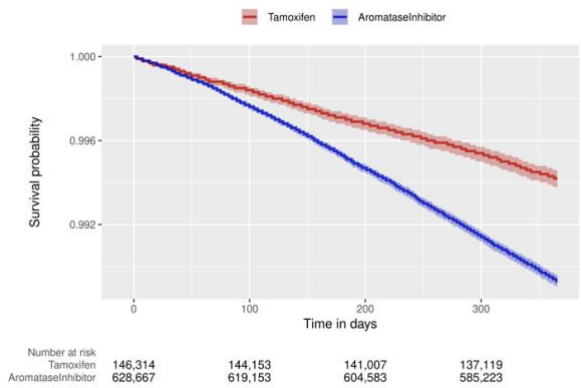
CPRD



SIDIAP



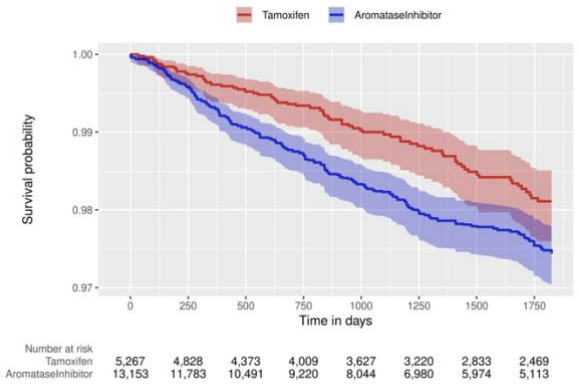
Hospital Charge DataMaster



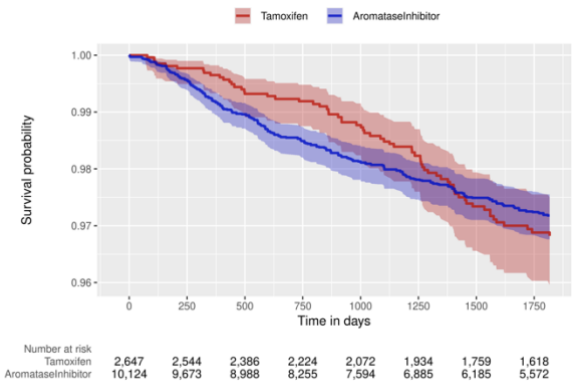
OpenClaims

Figures 8.11-14 Kaplan Meier plots for medical CTS outcome, ITT 1 year analyses

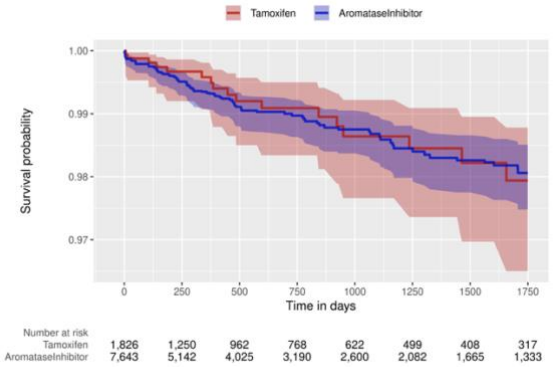
8.4.3.5 Medical CTS- ITT 5 year analysis



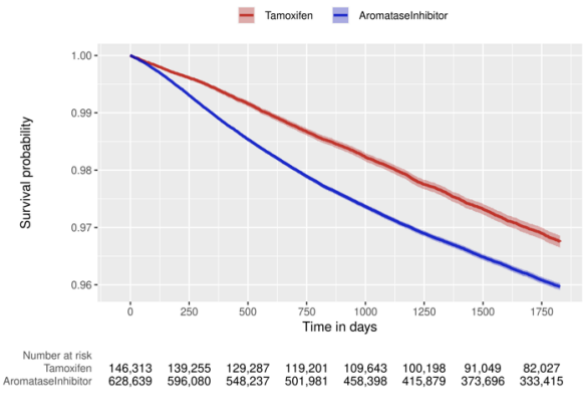
CPRD



SIDIAP



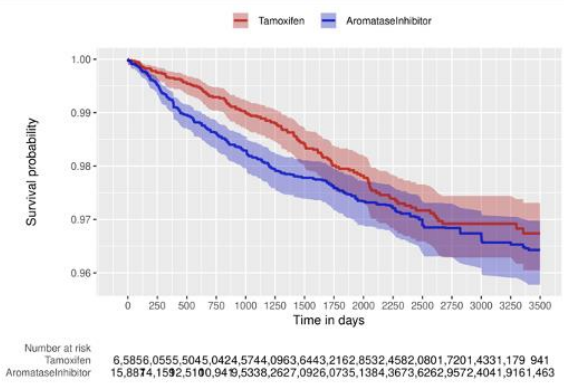
Hospital Charge DataMaster



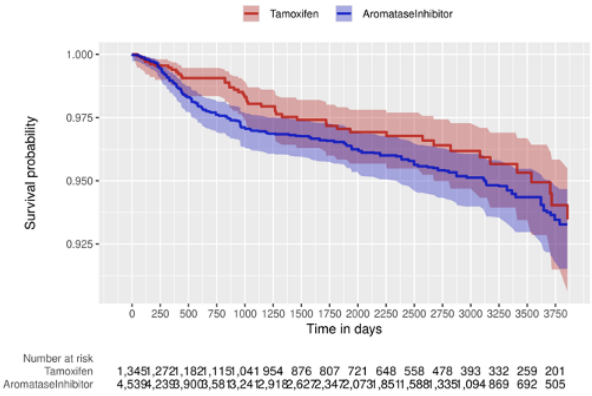
OpenClaims

Figures 8.15-18 Kaplan Meier plots for medical CTS outcome, ITT 5 year analyses

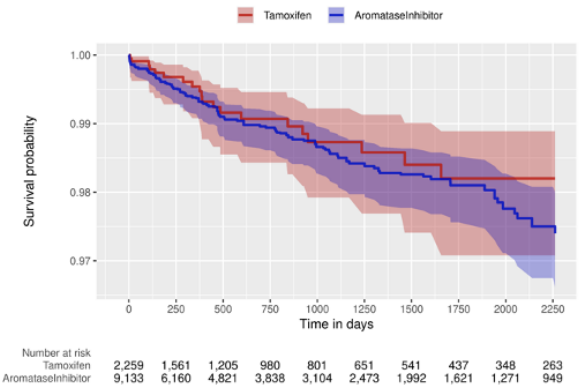
8.4.3.6 Medical CTS- On treatment analysis



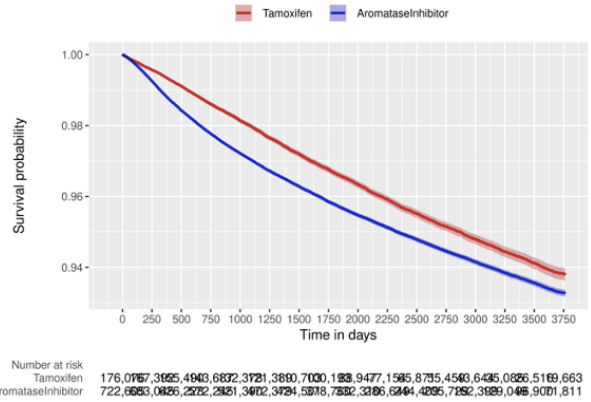
CPRD



SIDIAP



Hospital Charge DataMaster



OpenClaims

Figures 8.19-22 Kaplan Meier plots for medical CTS outcome, OnTreatment analyses

8.4.4 Secondary analyses

8.4.4.1 Non-steroidal vs Steroidal Aromatase Inhibitors

In the analysis comparing steroidal exemestane with the non-steroidal azole based AI drugs, only Open Claims was sufficiently powered to undertake the analysis (Figures 8.23 and 8.24) An increased risk of both medically and surgically treated CTS was seen for exemestane compared to azoles, especially in the short term ITT analysis [Medical

CTS: ITT 1year HR 1.30 (95% CI 1.19-1.42; 642 cases/50 879 in new users of steroidal versus 2425 cases/248 165 in new users of non-steroidal AIs); ITT 5 years HR 1.17 (1.11-1.24; 1749/ 50 882 vs 7700/248 186); On treatment HR 1.14 (1.09-1.19; 2569/65 877 vs 11 456/301 751): Surgical CTS ITT 1 year HR1.41 (1.22-1.63; 239/ 51 025 vs 820/ 248 902); ITT 5 years HR 1.18 (1.08-1.28; 687/51 030 vs 3005/ 248 924); On treatment HR1.14 (1.06-1.22; 1031/ 66 271 vs 4648/ 303 612)]. An increased risk of incident medical BTOA was also seen with steroidal AI use [ITT 1 year HR 1.30 (1.05-1.59; 117/51 061 vs 442/249 054); ITT 5 years HR 1.21 (1.09-1.33; 526/51 064 vs 2274/249079); On treatment HR 1.15 (1.06-1.24; 1035/66 371 vs 4849/304005)]. There was insufficient power to test for the association with incident surgically treated BTOA.

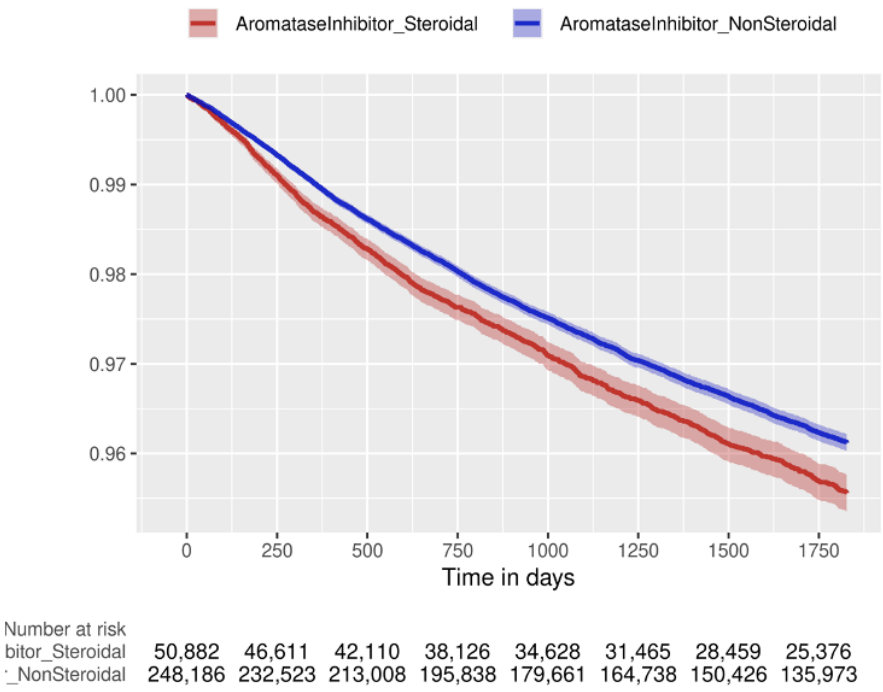


Figure 8.23 Association of Steroidal AI use versus Non-steroidal AI use with incident medially diagnosed CTS, ITT 5y

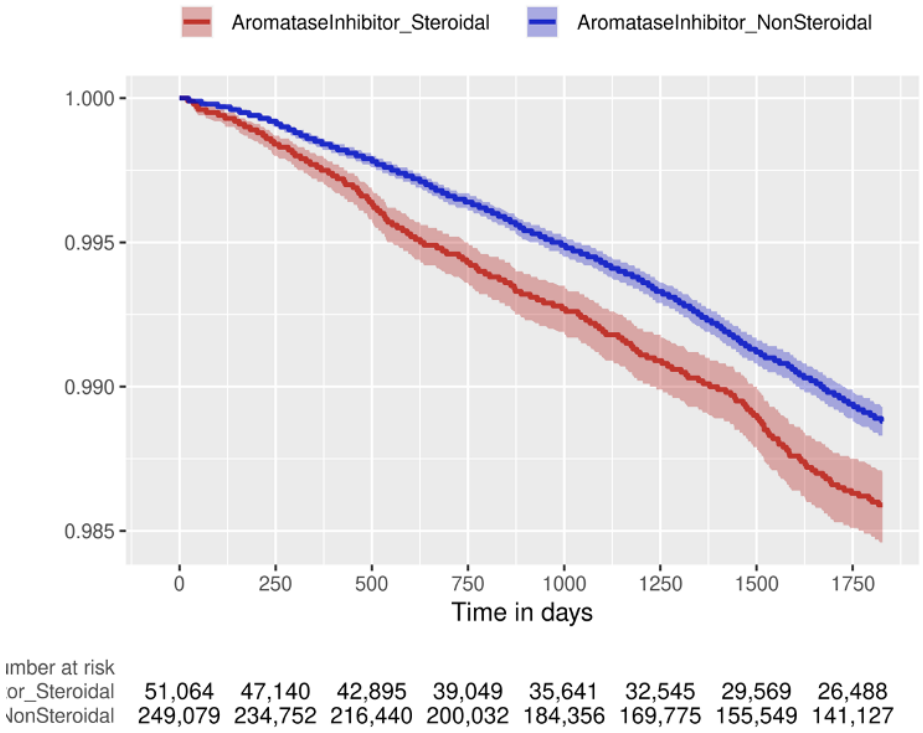


Figure 8.24 Association of Steroidal AI use versus Non-steroidal AI use with incident medially diagnosed BTOA, ITT 5y

8.4.4.2 Excluding Bisphosphonate users

Secondary analyses excluding concomitant users of bisphosphonates passed study diagnostics in all four datasets included in the main analysis. Hospital Charge DataMaster SIDIAP, Hospital Charge DataMaster and OpenClaims were able to contribute to the ITT one year analysis, with all four datasets contributing to the On Treatment and ITT five year studies (Figure 8.25). Similar associations were seen as were found in the main medical BTOA analysis, with an association of incident medical BTOA seen in the ITT one year analysis that was attenuated with five year follow up and no association found with an on treatment approach. Again, OpenClaims provided the majority of patients in the meta-analyses and was the main driver of the results (figure 8.25).

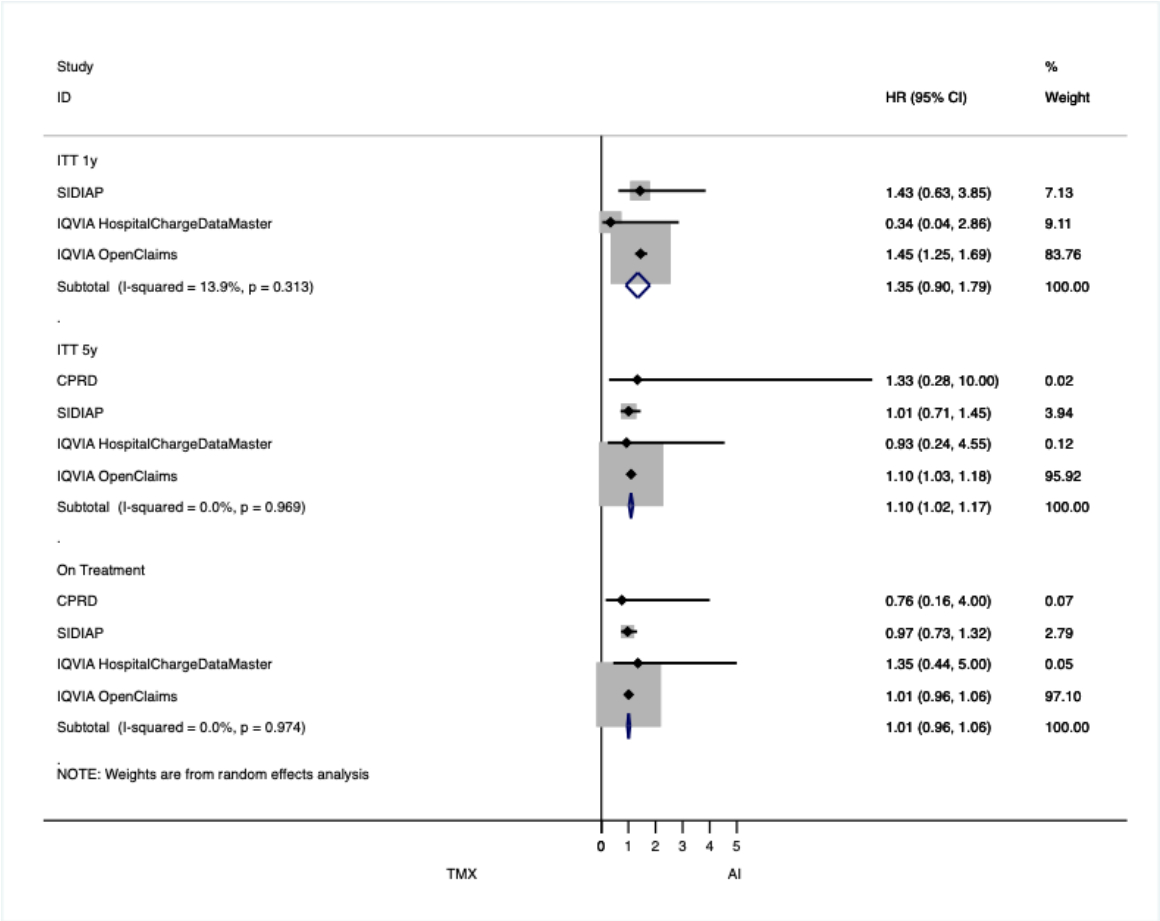


Figure 8.25 AI-TMX analysis excluding users of bisphosphonates and association with incident medically treated BTOA, results of three analytical designs with meta-analyses.

8.4.4.3 2015 study start date

Unfortunately, Hospital Charge DataMaster did not pass study diagnostics for this analysis designed to further interrogate the potential coding bias of ICD9-10 conversion in US data sources. This was due to poor covariate balance and power. OpenClaims passed diagnostics to contribute to all analysis designs for CTS and medical BTOA but only on treatment analysis for surgical BTOA.CPRD and SIDIAP were able to provide comparison to trends in European data in the on-treatment design only. All associations in these analyses concurred with the main study, with slightly stronger associations suggested for incident disease with AI use (e.g. HR 2.38 (1.96-2.94; 97 cases/ 58 102 new users TMX vs 1062/269 009 new users of AIs) for 2015 analysis for CTS surgical outcome, ITT 1 year in OpenClaims versus HR 2.22 (1.96-2.56; 242 cases/146623 vs 2338/629996) in main analysis). Overall, this analysis was relatively underpowered for drawing meaningful conclusions surrounding the coding of surgical procedures due to the rare incidence of surgically managed BTOA.

8.5 Discussion

8.5.1 Key findings

Increased risk of medical and surgical CTS was seen in post-menopausal women who are new users of aromatase inhibitors versus tamoxifen. This was particularly prominent in the ITT short term one year follow up analyses. BTOA was a rare incident outcome, with only the medically defined BTOA outcome able to run in most datasets. No association of medical BTOA was seen in with either drug use in all datasets but OpenClaims, where an increase in disease incidence was found in women taking AIs in

the ITT analyses. The increased risk associated with AI use was again more prominent in the short term follow up analysis. No association was identified with surgically treated BTOA, although this outcome was extremely rare. The relative magnitude of OpenClaims generated meta-analytic estimates that were driven by results in this dataset. This study therefore suggests that AI use is associated with increased CTS and medical BTOA, particularly within the first year of use.

This study identified the key areas required to lead a federated network analysis. Firstly, the need for a collaborative approach between research partners, ideally including researchers with a varying range of expertise. Secondly the need to project manage the study, developing study timelines, managing expectations and developing lines of communication. Finally, an open approach was needed to encourage collaborative research, leading by example through developing and running standardised packages with CPRD.

8.5.2 Strengths and Limitations

This study aimed to identify if signals found in RCTs were found in routinely collected data. It aimed to replicate a study across international datasets that included a variety of healthcare systems and healthcare data sets. This study aimed to do this in to more robustly evaluate causes of confounding and takes an observational study a step closer to identifying associations that may exist in routine care.

Using newly emerging standard analytical tools and a new federated network of data sources could bring cynicism from researchers appraising a OHDSI study for the first

time. The two shiny applications and open-source approach to sharing code were used to enable the study to be fully appraised. The interactive web-based platforms enable aggregated results to be shared between researchers and encourages interdisciplinary and inter-institutional discussion without sharing the data itself. The platform can also be kept live to assist with the peer review process, and to enable anyone to appraise the data generated in greater depth than is conventionally possible.

Cohort diagnostics enabled evaluation of study feasibility during design and increased the clinical face validity of the results. The ability to compare prevalence, incidence rates and characteristics of patients included in a cohort enabled the collaborators to identify if a study partner will bring a potential bias, or if the study design has flaws. Producing cohort diagnostics also served as a method of establishing feasibility of collaboration with the data partners themselves; their ability to engage and collaborate in a timely fashion, to run standardised packages and to assist in troubleshooting within the process. It served as a way for a group of international researchers from with a variety of expertise (clinical, data science) and backgrounds (academic, industry) who had never met in person to engage in the project together and develop a feeling of ownership.

EvidenceExplorer enables results to be appraised both blinded whilst evaluating if a data source is sufficiently robust to contribute to the final results, and unblinded to enable the direction of associations to be seen. This is particularly important considering the number of variations of analytical studies that were undertaken within this work and is a method of displaying results in a more user friendly, modern format.

This study attempted to address the potential weaknesses of observational research in its design. Use of an active comparator aimed to prevent confounding by lack of comparison or to untreated women, where large residual differences in baseline characteristics may exist between populations. Similarly, the use of negative control outcomes aimed to identify the risk of unobserved confounding.[17] Women with a diagnosis of breast cancer will interact with healthcare services differently from those women who do not, and outcome can only be detected should women present to healthcare services.

The study uses large scale data driven propensity score adjustment to address observed confounding. This confers the potential advantage of using all available data to balance the two exposure cohorts to better replicate the randomisation process in clinical trials. A limitation of observational research is that patient characteristics may influence treatment choice in real world data, and PS adjustment attempts to reduce this influence to average the probability of outcome occurrence between groups. A large-scale data driven approach uses thousands of potential candidate covariates to best balance groups and following PS adjustment the final balance was also appraised. Should a residual SMD persist, results were not included. This approach is one of the strengths of using a standardised analytical tool, as this computationally heavy methodology may otherwise be out of reach to most academic clinicians.

Limitations persist in study design. Confounding by indication may still exist for post-menopausal women prescribed tamoxifen compared to those prescribed aromatase inhibitors. Whilst every effort was made to address this potential bias by ensuring all women had a recent breast cancer diagnosis and had no secondary disease, without

information regarding why a clinical decision was made it is difficult to exclude any confounding in this area. Similarly the loss of power, and the trends seen on Kaplan Meier analysis in the longer analyses could suggest that 'depletion of susceptibles' may have an effect in the 5 year and on treatment analyses.[353] As women may cease to take medications due to side effects experienced, it appears that there is a reduced association with adverse outcome, when in fact the opposite is true. This phenomenon is suggested by the Kaplan Meier plots in SIDIAP, particularly in 8.4.3.5, but is also seen for BTOA in OpenClaims in Appendix G Figure G.18.

One must acknowledge the limitations of the OHDSI OMOP CDM and federated network design. Currently, the analysis cannot take account of the dose of medication used. This is less important for a drug study of cancer medications where doses are likely to be universal, but this may be a significant limitation in other pharmacoepidemiological studies. As the study is run as a federated network analysis with all data sources analysed at source, it is impossible to identify if a patient is present in more than one dataset. This is only likely to occur in the US datasets where overlap may exist, and by use of very heterogeneous datasets one reduces the likelihood of patients contributing data more than once.

Modifying standardised analytical packages reduces the risk of coding error, but also limits the versatility of analysis available. The CohortMethod package currently gives the option to use cox proportional hazards as the model for outcome but does not give the option to incorporate a competing risk analysis. This is pertinent for this study that is based in breast cancer patients who have a higher competing risk of mortality

than the general population. After discussion within the collaborative group and considering the five-year mortality for breast cancer is now quoted to be over 90%, it was felt that proceeding with initial outcomes based upon a cox proportional hazards model first was appropriate.[327] We are now working with collaborators in the group to design a competing risk analysis model, that will then be run in the datasets with mortality data as a sensitivity analysis. This also aims to give back to the OHDSI community, so that others may adapt the developed competing risk package in future studies.

Selection bias may be generated by requiring a certain period of observation within a dataset. A period of 365 days prior to new drug use was generated in order to ensure that exposure groups could be balanced appropriately and that women would be in the same period of their cancer treatment. Discussion with oncologists and breast surgeons noted that initiation of hormone blocking drug treatment was likely to be at least one year following initial diagnosis and surgery and therefore this arbitrary cut off was placed at this point. A lack of long observation periods within data sources is a particular limitation for datasets based in private healthcare and medical insurance, predominantly in the US data sources. The attrition of included women was evaluated in cohort diagnostics prior to making the final exposure definition in order to address selection bias as much as possible.

Incorrect classification of exposure, outcome or covariates remain a potential source of bias in observational studies. Time was spent on developing cohort definitions, iterating and leading collaborator discussions in attempts to reduce this risk. The

secondary analysis restricting the study period from 2015 onwards aimed to investigate this further but had limited value in this sub selection of datasets with these relatively rare outcomes. Misclassification though lack of primary adherence to a prescribed medication exists as a potential risk, although it could be suggested that adherence to a medication prescribed to prevent cancer recurrence and survival may have better treatment concordance than with drugs in other areas. Similarly, if patients do not present to healthcare services with symptoms associated with CTS or BTOA, this will not be identified. In this sense, this study can only identify associations with medically and surgically significant CTS and BTOA and the more severe symptoms of disease.

Menopausal status is not a covariate found in routinely collected data. Unlike the study in chapter 7, this OHDSI study assumes post-menopausal status based upon age. This may exclude younger, post-menopausal women from the analysis through restriction of the cohort. This highlights that any other potential risk factors for disease development such as occupation or lifestyle factors could not be included in this analysis. Negative control outcomes were used in order to suggest if residual unobserved confounding existed, but again, this can only be based upon data existing in the data sources.

8.5.3 Comparison to other studies

This work aligns with the results seen in the original RCTs where CTS incidence was explored in secondary analyses. [215, 216, 301] Further granularity of disease severity, and comparison with other types of hand condition such as BTOA was not undertaken and

therefore this study adds some suggestions of disease pathogenesis. Other lower levels of evidence had also suggested an association of CTS and BTOA with oestrogen deprivation but had not appraised the association with breast cancer medications in observational data. [335] The evidence generated in Chapter 7 of increased incident CTS and BTOA associated with oophorectomy appears to align with the increased incidence of disease here associated with oestrogen blockade.

8.5.4 Interpretation and Generalisability

These results are part of a larger, general study of musculoskeletal adverse events associated with AI run within this collaboration. The larger study has also investigated OA at other anatomical sites and the incidence of tendinopathies. Medically treated tendinopathy also appears to be associated with AI use, particularly in the hand and wrist (Figure 8.26). This aligns with prior evidence in the literature of the increased incidence of tendinopathy following AI use, but only at case reports or case series.[354, 355] Considering that the incidence of BTOA was low and did not appear to be associated with AI use overall, this could suggest that CTS is generated through a similar inflammatory process.

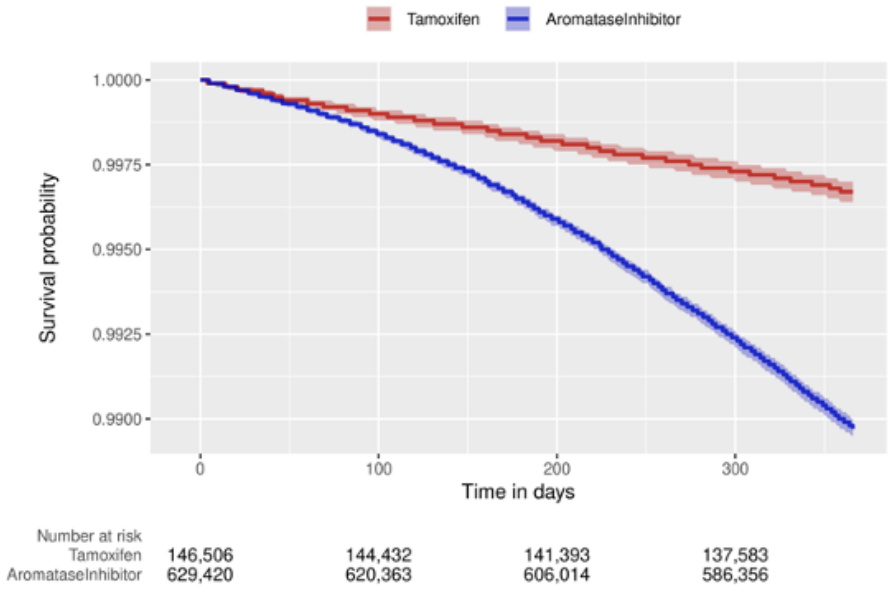


Figure 8.26 Kaplan Meier plot for hand and wrist tendinopathy outcome, openclaims ITT 1 y

8.5.5 Future research

Residual confounding remains an issue for observational research. In the context of this study and the evidence of increased survival with the use of AIs, it would be unethical for future RCT study to evaluate the risk of hand conditions such as BTOA generated as a side effect. An option that has been proposed to minimise residual confounding due to imbalances in unobserved covariates is empirical calibration based on negative control outcomes. This could be undertaken to compare database specific hazard ratios and 95% confidence intervals using identified negative control outcomes to generate an empirical null distribution.[356-358]

Other collaborative partners from Janssen and Stanford have offered to participate in this study and may run the analyses in future, to note the results found in further datasets.

Further work will also focus upon an adapted version of the analysis to incorporate the competing risk of mortality. This will serve as a proof of concept for the designed package for the OHDSI community, but also as a sensitivity analysis within this study to confirm the impact of mortality upon incident musculoskeletal disease. This element of further work epitomises the nature of the OHDSI network, emphasising the opportunity for symbiotic work that builds upon the diverse skills of the community to improve future research efforts.

9. Discussion

The modernisation of medical care, in particular the use of electronic health records, offers the great possibility of observational research with widely available data. The speed of data availability does not appear to be matched by a critical appraisal of the data and healthy scepticism of the role of routinely collected data sources in generating meaningful clinical evidence. This work aimed to identify, analyse and appraise multiple data sources for modern surgical epidemiology. It used the surgical management of two common hand conditions, carpal tunnel syndrome and base of thumb osteoarthritis as exemplars to explore the utility of routinely collected data. The clinical and methodological foci aligned in generating two broad areas of work; appraising the benefits and risks of surgery in routine clinical practice, and to develop a better understanding of the role of female hormones in disease aetiology.

9.1 Summary of findings

9.1.2 Data sources

In chapter 2 the setting and content of each included data source was appraised alongside the advantages and disadvantages of each. I emphasised the broad national perspective brought by the surgical trends and serious complications able to be studied in administrative data like HES APC. The major limitation of this dataset is that it cannot identify any outcomes that do not generate an in-patient admission. Surgical registries like UKHR can provide greater detail of the surgical procedure and detailed outcome measurement using PROMs, but are limited by a lack of demographic details, comorbidities or previous treatments if generated in isolation from an administrative

data source. Similarly, a small registry without clear indications for why patients are included, can also be limited by selection bias. Prospective cohort studies such as MWS repurposed for orthopaedic surgical research offer the exciting ability to stretch outside of the conventional orthopaedic paradigm. This offers the ability to use rich phenotypic data but requires linkage to routinely collected data to identify surgical outcomes outside the original scope of the cohort. Studies using repurposed cohorts are therefore reliant upon adequate validation work to identify surgical outcomes in routine data. Federated network analysis offers the opportunity to align international data sources using large scale analytics in standardised processes. The use of a common data model between data sources enables streamlining of analysis and efficiency of collaboration. As all data remains at source, a lack of granularity in each data source requires prior work to develop an appropriate study design, especially the key elements of exposure and outcome.

For all data sources, data quality assessment is vital through careful validation to determine if a generated definition truly represents a clinical phenomenon. Data processing and analysis methodologies were described as a key element of evidence replication for other researchers and a part of an open science process.

9.1.3 Trends in CTD practice: an introduction administrative secondary care data

In chapter 3 I used a 19-year bespoke cut of individual patient data to generate a greater evidence base for the risks of surgery, to better inform patients at the point of consent. In over 855,000 primary surgeries I demonstrated a bimodal distribution in primary surgery for women with a perimenopausal peak that stimulated further

analysis of CTS aetiology in later chapters. This work identified 3.42% CTDs (n= 29 288/855 838) proceeded to revision compression in England, with median time to reoperation of around one year. Increased risk of revision was associated with male sex, increasing comorbidity, increasing age and social deprivation. Overall rates of serious complications were low at 0.08% (n= 698/ 855 838) within 90 days, with male sex and younger age associated with increased relative rates of complications despite their overall scarcity.

This work also provides data that could be used clinically to enable comparisons of surgical centres against a national average.

From a methodological perspective, I also performed a detailed validation study in HES APC both for CTS but also for post-operative complications of musculoskeletal local anaesthetic procedures. This supported work with collaborators within NDORMS and has subsequently been used to promote further work in administrative data in hand surgery nationally. This work in collaboration with BSSH aims to drive improvements national standards in clinical coding to enable future research and audit of national hand surgical activity.

9.1.4 Assessing treatment pathways and the risk of serious adverse events in patient sub cohorts: further analysis in administrative secondary care data

In chapter 4, I built upon the foundations established in Chapter 3 to interrogate HES APC in more detail. This work aimed to determine if it was possible to identify the treatment pathway of those undergoing BTOA injection, to identify BTOA surgical subtypes and to compare the risk of serious adverse events in each cohort.

Clinically this chapter provided evidence based upon 19,000 'primary' BTOA injections delivered in radiological or surgical settings in secondary care and over 43 000 primary BTOA surgeries. Nationally, 50% (n=9651/19 120) of those undergoing BTOA injection went onto a further intervention and 22% (n=428/19 120) went onto surgery, with a median time to intervention of around 18 months. Multivariable analysis suggested a reducing trend in further intervention at extremes of age and with increasing levels of comorbidity. Only 0.04% of BTOA injections were identified as sustaining a serious complications requiring hospital admission within 90 days.

After three validation studies, I was able to confidently identify surgical subtypes undertaken for BTOA in an English national cohort. Most surgeries identified in HES APC were simple trapeziectomies, which suggests that practice in the English NHS is aligned with RCT evidence that shows no benefit of additional procedures beyond trapeziectomy (such as LRTI). There is currently much debate in the clinical community about the role of newer innovations such as arthroplasty in the treatment of BTOA, but this work suggests caution due to higher rates of revision in comparison to trapeziectomy. This work suggests an overall reoperation rate of 1.39% (n=599/43 076), but a rate of further procedure following BTOA arthroplasty of 3.84% (n=63/1 640). Multivariable regression identified that this risk of revision was 2.5 times that of simple trapeziectomy despite adjustment for age, sex, comorbidity, or socioeconomic deprivation. Whether this reflects the surgical learning curve, a variety of surgical implant survival or confounding by indication is an important question for future research.

Local and systemic serious complication rates at 90 days after BTOA surgery sat at 0.3% (n=87/ 43 076) and 0.6% (n=250/ 43 076) respectively. Historically BTOA surgery has been undertaken under general anaesthetic, and this work adds to the clinical debate surrounding the progression of hand surgery towards wide awake local anaesthetic no tourniquet (WALANT) techniques. Considering the risk of systemic complications for treatment of a non-life-threatening condition, I suggest that this procedure should be undertaken under WALANT or regional anaesthesia in future to mitigate these risks.

From a research perspective this work provided additional validation studies exploring surgical subtype and systemic complications associated with a general anaesthetic procedure. It highlights the potential issue with isolating different disease aetiologies within a general condition like BTOA, where without granularity of coding, post traumatic OA and generalised degenerative OA cannot be differentiated in routinely collected data. The inability to identify the indication for surgery remains an unsolved problem for this type of study design. The interplay of the surgical device used, surgical ability, hospital and healthcare system factors adds an additional layer of complexity that cannot be addressed by current analytical techniques. Future work should address from a methodological perspective, particularly by combining routinely collected data sources. The trend of increasing rates of surgery over the 19 year-period for BTOA compared to a flat trend for CTS emphasises the difference between CTD and BTOA surgeries politically in the NHS during this time. One factor which may have influenced these contrasting results is the impact of restrictions upon surgical

activity placed for CTS. Further research into the impact of policy upon hand surgery would be pertinent to explore this further, in addition to external validation of results found in England within the devolved nations.

9.1.5 Patient reported outcomes and bespoke surgical registries

The assessment of patient reported outcome following simple trapeziectomy versus trapeziectomy with ligament reconstruction represents the first peer review published work to quantify whether there is any value in surgery for BTOA in routine clinical care. Clinically this work adds to the literature by identifying a significant improvement following both types of surgery in both general and hand specific quality of life with no difference between procedures. The greatest improvement is seen in the first three months after surgery, which aligns with treatment effects seen in other areas of musculoskeletal surgery.

My work in chapter 5 represents the first research output from the UKHR and has demonstrated to the hand surgery community what is possible from this resource. It opens discussion about how clinicians should proactively promote research in this area to identify if surgery does improve quality of life. Future research using this type of data will generate patient-relevant results to enable surgeons to discuss continuing their work in the NHS. In future, patient focussed outcome comparisons with non-surgical treatment in routine clinical care are still needed. Loss to follow up remains an issue, especially here in the UKHR even though baseline completion was good. Moving forward researchers and clinicians need to be better at addressing loss to follow up to generate more complete evidence for patient focussed outcomes.

9.1.6 Evidence from the literature for disease aetiology

The two systematic reviews in Chapter 6 set the scene for the work in chapters 7 and 8. They emphasise the importance of age and sex in BTOA disease development along with BMI in CTS. The strong signal for the role of aromatase inhibitors in the development of CTS led to the generation of the research question studied in chapter 8. The lack of consistent evidence for the impact of endogenous female hormones upon disease development stimulated the question asked in Chapter 7 and emphasised the significant role of confounding in unravelling the role of female hormones in disease incidence.

9.1.7 Determining the impact of endogenous female hormones upon the need for surgery: a prospective cohort study linked to administrative secondary care data

My work in chapter 7 found an increased risk of CTS was associated with early menarche, an increased number of full-term pregnancies, and bilateral oophorectomy. Undergoing oophorectomy at an early age was associated with a 50% increased relative risk of CTS and twice the relative risk of BTOA, with early age at menopause not being a significant factor for those experiencing a natural menopause. Clinically, this suggests a need for counselling at point of consent of oophorectomy.

From a research perspective, this work in MWS emphasises the importance of prospective collection of additional data that is not recorded in routine data to answer

questions that would not be possible in routine datasets alone. It also emphasises the important of linkage to another data source to identify outcome when repurposing data already in an existing cohort study. The use of MWS for a different research field (musculoskeletal) from which it was originally intended (cancer) identifies the value of collaboration between clinicians and scientists from various disciplines. This enables research to draw parallels and associations at the border of other clinical fields that may not have otherwise been identified.

9.1.8 Determining the adverse events associated with female hormonal blockade: international federated network analysis including UK primary care data

Clinically the evidence I generated in Chapter 8 identified an increased risk of CTS and BTOA in women who are new users of aromatase inhibitors. This increased risk of hand conditions is mostly seen early in treatment and was replicated in three countries in an analysis of just under one million women. A relative risk of 1.8 to two-fold for CTS in new users of AIs was seen at one year following initiation of treatment, with a 40% increased relative risk of BTOA. This appears to be driven by a tendinopathic process rather than a degenerative process considering the increased risk of hand and wrist tendinopathy also seen. This study using routinely collected data reveals the same direction of effect as seen in early RCTs for AI use that focussed upon their impact on cancer survival and recurrence. When comparing my results in Chapter 8 back to literature, figure 1 from Sestak *et al.* showing CTS development in AI RCT participants was strikingly similar to the results I found.[300] This emphasises the early development of musculoskeletal adverse events, and the importance of a new-user

and intention to treat design to enable the interface of observational and clinical research.

The work in chapter 8 demonstrated the possibility of conducting surgically focussed research in EHDEN/OHDSI community. This was possible as a new entrant to the community through the use of standardised tools to facilitate international collaboration. This study emphasised the importance of iterations in study design within the group of collaborators to best generate exposure and outcome definitions, and that is particularly important in this federated network approach. This study also identified the restriction in available analysis designs and the potential disadvantages due to the need to use standardised analytics. It emphasised for me the importance of identifying these areas not currently covered by standardised analytics as a focus for future development in the community.

9.2 Implications for clinical practice

Overall, the information from this thesis provides evidence for informed consent and shared decision making for CTD and BTOA surgery and for intra-articular BTOA injection in secondary care. It used data from routine clinical care to provide more generalisable results for use in everyday practice. I have provided examples of how data can be used to identify the risk-benefit trade off in surgical treatments. Evidence generated can be used to drive improved standards of clinical care in the NHS through providing a national benchmark of outcome. This thesis generated evidence supporting the use of surgery in the treatment of BTOA from the patient perspective and stimulates further discussion in the surgical community surrounding the role of

simple trapeziectomy compared to that of more complex procedures. Whilst the overall risk of revision surgery is low, this thesis proposes that further clinical research is needed to better define the comparative risk and benefits of arthroplasty for BTOA compared to the conventional trapeziectomy. This work has reached out to repurpose data to better understand surgical disease aetiology through crossing clinical paradigms. This has emphasised the disadvantage of tribal nature of clinical medicine, where a lack of integration between clinical specialties prevents shared knowledge. This thesis aims to take this forward as a learning point, to promote research as a driver for future discourse between clinical subspecialties that have shared patient populations.

9.3 Implications for research practice

Work I have completed in this thesis suggested the potential value of routinely collected data for orthopaedic research and the potential for it to interface with clinical research specialties. Administrative data has a role in overall analysis of trends in surgical practice, with implications for surgical policy development. It can also augment prospective cohort studies, especially in repurposing data that may not have been focussed upon orthopaedic outcomes. The value of a surgically focussed registry is shown within this research. This work opens discussion surrounding the implementation of national collection of PROMs to prevent the selection bias seen with voluntary recruitment. This would not just add to the ability to generate evidence, but also reframe outcome following treatment towards patient reported outcome rather than serious adverse events as a proxy, clinically focussed metric. Finally, this thesis suggests that international collaboration associated with data

harmonisation in an open science approach offers a sustainable resource in a post pandemic era, especially for areas like orthopaedics.

9.4 Limitations and Future work

This thesis highlights the importance of further research into how to implement multilevel modelling for surgical and device epidemiology. The interplay of many levels of factors in surgical risk factor association studies adds a layer of complexity to identifying associations in routinely collected data. Methodological work in this area would offer huge benefits to future research. Considering the examples of serious adverse events associated with the use of devices in other areas of orthopaedics, a limitation of this thesis is an inability to appraise specific devices used. Further work should prioritise the large-scale identification and assimilation of device data with data from routine clinical care.

For trends in outcome following surgery, this thesis has not been able to appraise the rate of adverse events outside of hospital admission. Future work should focus on identifying complications presenting in a primary or intermediate care setting. This would enrich the evidence base for the spectrum of adverse events that can occur and identify equally important outcomes such as complex regional pain syndrome and surgical site infections treated by antibiotics alone. Better integration between primary, intermediate and secondary care data may also enable better understanding of the patient treatment pathway prior to secondary care.

For the trends in surgical treatment, external validation would strengthen the evidence found in the English NHS. This could be undertaken within administrative care datasets in the devolved nations, or through comparison to other administrative secondary care datasets internationally. Similarly, no comparison with non-operative treatment has been undertaken in this thesis. Better integration of available intermediate and primary care data as the modernisation of medical data continues will offer possibilities of large scale data collection for the use of physio and occupational therapies.

For risk factor association studies, the time varying impact of HRT upon the role of endogenous female hormones has not been explored. The analysis of the competing risk of mortality in the analysis of the association of hand conditions with new use of aromatase inhibitors has also not been undertaken. These represent more complex epidemiological analyses that are beyond the scope of this work but remain important for our understanding of female hormones and hand conditions. The data generated in patient reported outcome measures following surgery could also be used as the basis for a cost effectiveness analysis.

My work has also identified the possibility for modern surgical epidemiology, to generate a hybrid approach to clinical research by integration with clinical trials. With appropriate validation, case generation and dynamic generation of available data associated with routine clinical care, routinely collected data offers the potential for enhanced identification of potential trial candidates, assimilation of automated data accrual, and a data driven approach to identifying appropriate recruitment sites.

Overall, this thesis emphasises that modern surgical epidemiology is a rapidly advancing field. Data generation is exponential, and the possibilities for integration on an international stage are possible more now than ever. In a post COVID-19 era, cloud-based technology, rapid generation of new innovations, and a paradigm shift in clinical medicine's desire to question the status quo has emerged. As we retreat back into our previous tribal clinical silos, one wonders if there has been a much greater potential for patient benefit in our apparent social isolation than the research community realise.

9.5 Post-viva addendum- take home messages

This section has been added following viva voce examination to highlight the key limitations of the data and analysis presented, and how these limitations could be in addressed in future research.

9.5.1 Chapter 2 limitations

- Validation studies supporting the work in HES were unable to identify false negatives.

Whilst I was able to identify cases misclassified as surgeries when one had not occurred, initially identifying cases through UK Biobank or the Million Women Study could never identify those who had surgery but were not coded as such. Future validation work could be augmented with a local study starting with operating theatre records of surgeries undertaken, and then identifying how these clinically confirmed

surgeries were coded. This would generate a more complete picture of coding accuracy.

9.5.2 Chapters 3 and 4 limitations

This work using HES administrative data has several key limitations:

- Lack of standardised national coding practice.
- Coding being driven by remuneration.
- Coding definitions have a major influence on populations defined and conclusions drawn.

For CTS, I decided how to define surgery for acute and chronic disease; for BTOA, code combinations for surgical subtypes had to be generated *de novo*. With the help of an experienced and multidisciplinary team, I developed code sets over several iterations, using clinical knowledge to attempt to reduce misclassification bias. However, there is no clear guidance about how these surgeries are coded.

- Past medical history in HES can only be identified if coded in a prior secondary care episode.

This means that prevalence of some diseases is likely to be underestimated, although conditions that increase the rate of remuneration may be more accurately identified. Furthermore, the true date of disease onset is difficult to determine. It is also likely that HES only captures those presenting with the most severe disease phenotype, as they have required secondary care management. This limitation can be overcome in future by research in linked primary and secondary care data sources, or through studies in primary care data sources to compare these associations found in secondary

care.

- The impact of research or changes in NHS policy upon practice is not fully considered.

I did not investigate the potential interaction of NHS policy, or the release of seminal clinical research that may drive surgical behaviour upon the incidence of surgery. However, I did attempt to compare trends in practice to those undertaken in other healthcare settings to unpick the potential causes or biases within trends seen in HES data. At the time, the PearlDiver analytic database (PearlDiver Technologies) of aggregated US insurance and Medicare data was the most easily accessible national data to use for comparisons. However, the aggregated nature of this platform made drawing conclusions difficult and the work was therefore not included in the thesis.

Investigating the impact of key policy change and release of clinical studies using interrupted time series analysis should be an area of future research. This would identify the potential cause for change in the healthcare system's ability to undertake surgery, or in a change in the surgical mindset altering the decision to proceed with surgical management. Work comparing administrative data from a variety of countries or data sources, for example using a federated network analysis, would also enable more generalisable conclusions about trends in surgical incidence to be drawn.

- The inability to identify a true denominator upon which to calculate surgical incidence.

Surgical incidence in Chapters 3 and 4 was determined using English population estimates as the denominator. This is a significant limitation, since HES APC will only identify surgeries undertaken within the NHS, and cannot estimate the volume of work undertaken privately. Similarly, HES only contains data from secondary care without information of interventions undertaken in intermediate care, which is particularly pertinent when considering steroid injections for CTS or BTOA. Future work in national administrative datasets should extend into identifying intermediate care provision and the volume of interventions undertaken both in this environment and within the private sector. This would also enable comparison between NHS secondary and intermediate providers, and private care environments. Such comparisons are timely as there is a current shift towards increasing the use of intermediate and private care providers for elective surgery in the wake of the Covid-19 pandemic.

- The identified ratio of trapeziectomies to LRTIs undertaken is not discussed in detail

In this thesis, in depth discussion of the numbers of trapeziectomies and LRTIs undertaken is not included, which is particularly important when considering the very different ratios of the two procedures found in chapters 4 and 5. Which source is incorrect? Whilst some informal discussions with hand surgeons suggested UK practice was more likely to be reflected by HES rather than the UKHR – i.e. most surgeons perform simple trapeziectomy – I cannot be certain of this.

Future work refining national coding practices, especially for BTOA, would address some of these limitations, and potentially improve use of NHS resources. Future work

should address how HES coding might drive change to a more evidence-based practice. Possible mechanisms include incentivising surgeons and NHS hospitals to mandate data collection, or automating data generation. This data can then be used as part of quality improvement, or dashboards to identify surgeon or unit-level performance, with the parallel aim of improving data quality for research.

9.5.3 Chapter 5 limitations

- Selection bias

The very major limitation of the UKHR dataset is selection bias. There is no information as to which surgeons have entered data into the registry, and which patients they have added to the dataset.

- Loss to follow-up

The loss of patients to follow-up is the second major limitation of UKHR, and is common to many registry studies.

I made efforts to compare PROMs following BTOA surgery in the UK with those undertaken by Xpert clinic, a chain of private hand surgery clinics in the Netherlands that undertake research within the Hand and Wrist study group at Erasmus MC University, Netherlands. Unfortunately, the surgical workload in the Netherlands consisted almost exclusively of LRTI with very few simple trapeziectomies undertaken. The UKHR study could therefore not be replicated, and this work was omitted from the thesis.

Future work in surgical registries should focus upon methods to ensure more complete case ascertainment from all hand surgeons nationally. This may require mandatory completion – perhaps utilising financial incentivisation of NHS hospitals to support their surgical teams in entering eligible patients. Ensuring completeness of follow-up is a difficult issue, and the UKHR has improved the electronic collection of PROMS data recently. The effect of this change will be evident in the coming years. Future work in small surgical registries should *apriori* identify areas of potential selection bias prior to analysis, to gain more clarity about why surgeons do or not participate or why patients may be lost to follow up. It will be interesting in future work to compare results from UKHR to other registries internationally. Linkage of data sources to augment bespoke surgically collected information and PROMs with routinely collected data, such as HES or primary care data, would also enable more meaningful results to be generated.

9.5.4 Chapter 6 limitations

As these systematic reviews focussed on disease aetiology, and there are two key specific limitations:

- Publication bias.
- Search terms generated only focussed upon risk factors identified within the title and abstract

My results are more likely to include studies with a positive association due to their greater chance of being published in the peer reviewed literature. Future systematic reviews of surgical disease aetiology should focus upon looking for risk factors buried as covariates in other epidemiological studies with a different specified outcome.

Furthermore, future reviews should include searches of work released outside of the peer reviewed literature. In particular, pre-print servers such as MedRxiv are gaining popularity in academic practice and searching and evaluating this literature will become more important in the future.

9.5.5 Chapter 7 limitations

The identification of surgical disease in MWS is based upon linkage of this large prospective cohort study to HES APC, and this work it is therefore limited by the same coding issues as described in section 9.5.2. However, it does have one other key limitation:

- Historic nature of the cohort

Whilst this work repurposes a robust prospective cohort study, one must also acknowledge the historical nature of the cohort, comprising women who were aged 50-64 when recruited between 1996-2001. The temporal changes in medical practice, and in particular HRT prescription over this time, may represent a significant source of confounding by indication. This is particularly important when considering the associations found for women undergoing oophorectomy at an early age. This group of women not taking HRT after oophorectomy may represent a very unusual group that have an unidentified cause of increased CTD or BTOA surgery. Future work should carefully consider the potential biases of any prospective cohorts linked to routinely collected data, and consider incorporating analysis of time varying confounding.

9.5.6 Chapter 8 limitations

The OHDSI study represents the most innovative work of the thesis. It is based on routinely collected data from multiple data sources, and as such suffers from the limitations associated with coding described in section 9.5.2. However, some limitations are mitigated by the effective replication of the analysis within different healthcare settings, representing different clinical and coding practices. The most significant limitation of this chapter is:

- My inability to express complex statistical methods, and to condense a large volume of data within a conventional format.

An example of this is the use of population characteristics within an interactive shiny application where an extensive set of baseline characteristics are included but are not as accessible as a traditional table of baseline demographics. Future work in federated network analyses, especially those using large scale analytics needs to focus upon communication of complex methodology including why methodologies were chosen, and why data sources were included or excluded. If infrastructures such as OHDSI are to emerge as robust sources of evidence in modern epidemiological research, greater formal consideration of how to present data in conventional formats, such as a thesis and a peer-reviewed publication, is needed to enable open discussion of their strengths and weaknesses.

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