Understanding the extent of, and reasons for, diagnostic delay in inflammatory bowel disease

Eleanor Cross

Master of Philosophy

2019

Understanding the extent of, and reasons for, diagnostic delay in inflammatory bowel disease

Eleanor Louise Cross

Master of Philosophy

Keele University

October 2019

Declaration

The outline of this research MPhil was proposed by my supervisor, Dr James Prior. Through discussions between myself and my three supervisors, Dr James Prior, Dr Benjamin Saunders and Dr Adam Farmer, the final research questions were confirmed.

I took the lead role during the completion of the systematic review. Assistance with the search strategy was provided by the systematic review team at the Research Institute of Primary Care and Health Sciences at Keele University along with my supervisors. Dr James Prior acted as the second reviewer during the title and abstract review. For the full-text review, Dr James Prior, Dr Benjamin Saunders and Dr Adam Farmer were second reviewers.

The structure of the qualitative research was created through discussion with myself and my supervisors. I recruited and interviewed all participants in this study, using a topic guide that had been devised through collaboration with Dr James Prior and Dr Charles Hay (research assistant, Keele University) and updated by myself. An independent transcription company and I completed the transcription of interviews. Audio recordings were stored within a secure drive and deleted following transcription. Transcripts were stored on a password-protected computer.

All of the findings from the systematic review and qualitative research are my own.

Abstract

Background: Inflammatory Bowel Disease (IBD) is a complex chronic condition affecting the gastrointestinal (GI) system and is sub-classified into Crohn's Disease (CD) and Ulcerative Colitis (UC). Patients with IBD can present with a multitude of symptoms, making the diagnosis challenging and frequently resulting in delays.

Aim & objective: The aim of this research was to better understand the extent of, and reasons for, diagnostic delay in IBD. The first objective was to establish the extent of which the diagnosis of IBD is typically delayed and any characteristics which may be related to this. The second objective was to explore the individual experience of delay, including possible contributing factors for delay as well as any impact of delay on the patient.

Methods: Two distinct methods were used. A systematic review was conducted to identify articles that reported a time-period of diagnostic delay of IBD. A narrative synthesis was then used to present the extent of IBD and explore consultation and healthcare factors for delay, which is defined below. Secondly, interviews were conducted with participants who self-reported a delay in IBD diagnosis, in order to explore this delay from their perspective. Participants were asked their opinions on factors which may have contributed to their delay and any consequences of this delay. Misdiagnoses they had been given before their IBD diagnosis was also discussed. Thematic analysis was applied to this dataset.

Results: For the systematic review, 7570 articles were sourced from the search following de-duplication. 5127 and 2143 articles were excluded following title and abstract review respectively. Of the remaining 284 articles for full-text review, 35 met the inclusion criteria. The median values of diagnostic delay were between 2 and 5.3 months for IBD, 2 to 26.4 months for CD and 2 to 12 months for UC. Consultation delays, defined as the time between the onset of patient symptoms and them seeking medical advice, ranged from 1 to 8.6 months in CD and 0.7 to 1.9 months in UC.

Healthcare delays, the time between patients seeking medical advice to receiving a diagnosis, were 0.7 to 20.8 months and 0.2 to 1.1 months for CD and UC respectively. From interviews with sixteen participants, irritable bowel syndrome (IBS), gastroenteritis and mental health conditions were commonly reported misdiagnoses. Participants cited a perceived insignificance of symptoms, fear and embarrassment as reasons why they delayed seeking medical advice. Patient-reported reasons for healthcare delays included GP reluctance to refer to secondary care and prolonged, ineffective management. Participants described experiencing issues with waiting lists for appointments and delayed diagnostic procedures. Some participants felt their delay had negatively impacted on their diagnosis, including a need for stronger medication or surgery.

Discussion: The overall diagnostic delay of IBD is extensive but varies considerably. Delay seems to be worse in CD than UC, particularly regarding healthcare delays. This is also supported by the interview findings.

Acknowledgements

I would like to extend my gratitude to many individuals, without whom, I would have been unable to complete this year. First and foremost, I thank Keele University for allowing me to intercalate. This opportunity to undertake this research has been valuable in many ways and I have learned far more than the content of this thesis.

I am immensely grateful to the participants who volunteered their time to share their experiences with me. Their experiences and insights have truly deepened my understanding of this subject.

To my supervisors James, Ben and Adam- I have greatly appreciated your unfailing support throughout this year. You have each allocated time during your busy working lives and beyond to help me through this year and I am immensely grateful for the wisdom you have shared. I have valued your assistance at every step during a rather lengthy systematic review and for your support and encouragement during the qualitative research.

In addition, I would like to thank the internal systematic review team at Keele University for their assistance during this challenging task. I also am indebted to my fellow postgraduate students, who have been an invaluable source of knowledge, inspiration and humour throughout this year.

I am endlessly indebted to the unwavering support from my fantastic parents, Nicole and Nigel. I have achieved everything in my life thus far because of your love, wisdom and encouragement. To my best friend and fiancé, Krystian- you have motivated me to lift up that laptop lid more than you realise! During the many challenges and moments of celebration this year has had to offer, you have all been by my side and guided me throughout. Finally, I would like to thank my tortoise, Truffle, for the quiet companionship during my hours in the study.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AF- Adam Farmer

BS- Benjamin Saunders

CD- Crohn's Disease

EC- Eleanor Cross

EIM- Extra-intestinal manifestation

GI- Gastrointestinal

GP- General Practitioner

GWAS- Genome Wide Association Study

IBD- Inflammatory Bowel Disease

IC- Indeterminate Colitis

IQR- Interquartile Range

JP- James Prior

MeSH- Medical Subject Headings

MRI- Magnetic Resonance Imaging

NC- Nadia Corp

NHS- National Health Service

NICE- National Institute of Health and Care Excellence

OB- Opeyemi Babatunde

PRISMA-P- Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PROSPERO- International Prospective Register of Systematic Reviews

RI- Research Institute of Primary Care and Health Sciences

UC- Ulcerative Colitis

1. Introduction

This thesis explores the extent to which the diagnosis of Inflammatory Bowel Disease (IBD), a chronic inflammatory condition affecting the gastrointestinal (GI) tract, can be delayed. Although there has been a considerable research effort into exploring the delays in diagnosis of IBD, this thesis aims to collate this data and build upon these findings in the form of a systematic review and novel qualitative research, in order to establish the extent of delay as described in the literature and investigate personal accounts of delay as experienced by people with IBD.

IBD is a relapsing-remitting condition characterised by chronic inflammation of the GI tract, meaning that symptom severity changes over time and therefore can give rise to acute exacerbations of symptoms. These are known as flares (Bernstein, 2015). Although there is no cure, management is largely aimed at reducing inflammation. The two most prevalent forms of IBD are Crohn's Disease (CD) and Ulcerative Colitis (UC). Whilst both are characterised by inflammation, the spectrum of symptoms, pathophysiology and distribution of disease differs considerably between CD and UC (Rosen, Dhawan, & Saeed, 2015). These conditions are discussed in more detail below and in the next chapter.

This chapter provides an introduction to IBD as well as the rationale for conducting research into delays in diagnosis. The aims of this research have been described along with the specific objectives.

1.1 An overview of inflammatory bowel disease

The aetiology of IBD is incompletely understood, though it is thought that a combination of genetic and environmental factors increase the risk of developing the condition (Khor, Gardet, & Xavier, 2011).

Typically, CD causes weight loss, diarrhoea, oral ulcers and perianal disease whereas patients with UC mostly experience rectal bleeding, abdominal pain and diarrhoea (Ghosh & Mitchell, 2007). There is significant overlap of clinical features between the two diseases and patients may not always present with clear, identifiable symptoms. Extra-intestinal manifestations (EIM) of IBD are symptoms that can occur before or after the diagnosis that are not limited to the GI tract. EIM include arthritis, dermatological conditions such as erythema nodosum, primary sclerosing cholangitis and uveitis (Vavricka *et al*., 2015). Again, these manifestations may conceal the true diagnosis of IBD.

As with many chronic conditions, IBD has the potential to negatively impact on an individual's quality of life (Ghosh & Mitchell, 2007). In addition, IBD is associated with higher levels of stress and depression (Zhang *et al*., 2016)

1.2 Diagnostic delay in inflammatory bowel disease

The diagnosis of IBD can be challenging, as presenting symptoms can be varied and readily mistaken for another condition. For example, people with IBD may experience a wide combination of symptoms including a change in bowel habit, abdominal pain and rectal bleeding, which could also be consistent with more prevalent disorders such as irritable bowel syndrome (IBS), gastroenteritis and haemorrhoids. EIM may also complicate an individuals' presentation. Additionally, in countries with a higher incidence of tuberculosis, IBD may be mistaken for abdominal tuberculosis which can prolong diagnostic delays (Das *et al.*, 2009). Diagnostic delays can also impede effective management.

Diagnostic delay is defined as a delay in receiving a diagnosis of health conditions from the time when symptoms for that condition begin, until a final diagnosis for that condition is provided by a healthcare professional (D.-W. Lee *et al*., 2017).

1.3 Rationale for this research

IBD has largely been considered a problem in high income countries, with approximately 2.5-3 million Europeans having the condition (Burisch, Jess, Martinato & Lakatos, 2013). However, research has also established an increasing incidence of IBD in areas previously considered less affected (Ray, 2016; Thia, Loftus, Sandborn, & Yang, 2008). As the global burden of IBD increases, it is important that people experiencing symptoms suggestive of IBD are investigated promptly and appropriately; and following diagnosis, are managed optimally.

IBD also exerts a marked socioeconomic burden, particularly as it largely affects the working-age population who, with severe disease, may be unable to work or require more frequent absence from work (Michael *et al*., 2014). Additionally, the healthcare costs of IBD are significant. For example, in a cohort study conducted by Bassi, Dodd, Williamson and Bodger which included 479 IBD patients at a university hospital in the Northwest of England, the total cost of care over the six month study period for this cohort was £757,433. Exacerbations led to a two- to three-fold increase in costs for outpatient care and over twenty-fold increase in hospitalised patients, compared to the cost of managing inactive IBD (Bassi, Dodd, Williamson, & Bodger, 2004).

There is evidence that diagnostic delays in IBD have a negative impact on the clinical course of disease. For instance, a retrospective study carried out by Lee *et al*. found that a delayed diagnosis of CD and UC was associated with an increased risk of intestinal surgery due to poorly-controlled disease (OR= 6.81; 95% CI= 1.12-41.4) (D.-W. Lee et al., 2017). A cohort study of CD patients in Korea also demonstrated a link between diagnostic delay of over eighteen months and worsening clinical outcomes, as there was an increased risk of intestinal stenosis (HR= 1.43; 95% CI= 1.07-1.93) internal fistulae (HR= 1.62; CI= 1.12-2.33) and perianal fistulae (HR= 1.38; 95% CI= 1.06-1.80) (Mo Moon C. *et al*., 2015). The increased need for surgery following a delayed diagnosis is likely to represent increased disease severity.

By conducting a systematic review, a benchmark value for diagnostic delay can be sought from existing literature, along with the identification of any important characteristics that may contribute to delay. This will clarify the impact of a delayed IBD diagnosis. Furthermore, specific individual reasons for diagnostic delay can be explored from the perspective of patients themselves through interviews, uncovering areas of improvement to reduce delay.

1.4 The aims of this thesis

The aim of this thesis was to explore the extent of, and reasons for, diagnostic delay of IBD at both a population- and patient-level. The specific objectives were:

1. To provide a benchmark time-period of diagnostic delay, from IBD symptom onset to IBD diagnosis, through the completion of a systematic review
2. To explore possible reasons for, and consequences of, diagnostic delay from the perspective of individuals who have experienced a delay in IBD diagnosis, through participant interviews

Combining a systematic review and qualitative study was seen to be the most effective means to address these research objectives. The use of two research methods to answer the research aims was influenced by a pragmatic methodology that has been adopted within this research. This pragmatic methodology is commonly used in mixed methods studies as it allows the freedom to choose different methods that are suited to the research objectives. Pragmatism is considered to be outcome orientated, meaning that methods are chosen based on whether they are most suited to answer the research aims (Morgan, 2007). This is in opposition to other methodologies with certain philosophical underpinnings where the choice of research methodology is dictated by the methods themselves (A. Brierley, 2017). Pragmatism was demonstrated in the decision to conduct a systematic review and qualitative research. The systematic review provides a comprehensive and

objective insight into diagnostic delay due to the structured method by which it was performed. On the other hand, the qualitative research in this thesis explores possible factors influencing delay and consequences of delay, from the perspective of individuals who have experienced this delay first-hand.

This thesis comprises a convergent mixed method design, whereby the results from the systematic review and qualitative research are analysed individually and subsequently combined to allow exploration of the research aims through joint interpretation (Fetters, Curry, & Creswell, 2013; Creswell & Plano Clark, 2011). This mixed method approach was beneficial, as the merging of results from two different methods strengthened the findings for diagnostic delay whilst being manageable within the time constraints of the MPhil, as the systematic review and qualitative research were conducted in parallel.

1.5 A summary of thesis chapters

The structure of the thesis is as follows. Chapter 2 provides a summary of IBD, including proposed risks, disease presentation, diagnosis and management as well as outlining delays in diagnosis. The methodology and results of the systematic review conducted within this thesis are self-contained within Chapter 3. Chapter 4 outlines the methodology of the qualitative research conducted, including justification of the decisions made during the research process. The results of the qualitative research are presented in Chapter 5. Chapter 6 provides an overall discussion of the findings, including their implications for clinical practice; as well as the author's reflections from completing this MPhil.

2 Background

Further to the information provided in the introduction, this chapter provides a more detailed overview of Inflammatory Bowel Disease (IBD), including the epidemiology, putative risk factors, diagnosis and management. An overview of some existing literature on delayed IBD diagnosis is also provided, though this is explored in greater detail within the systematic review in Chapter 3.

2.1 An overview of the digestive tract

2.1.1 Anatomy of the gastrointestinal system

The digestive system is made up of the gastrointestinal (GI) or alimentary tract along with accessory organs of digestion, including the salivary glands, liver and pancreas. The GI tract is formed by the mouth, pharynx, oesophagus, stomach, small bowel, large bowel (or colon), rectum and anus. Digestion, absorption and excretion are the main functions of the GI tract, along with playing a role in immunity (Reed & Wickham, 2009).

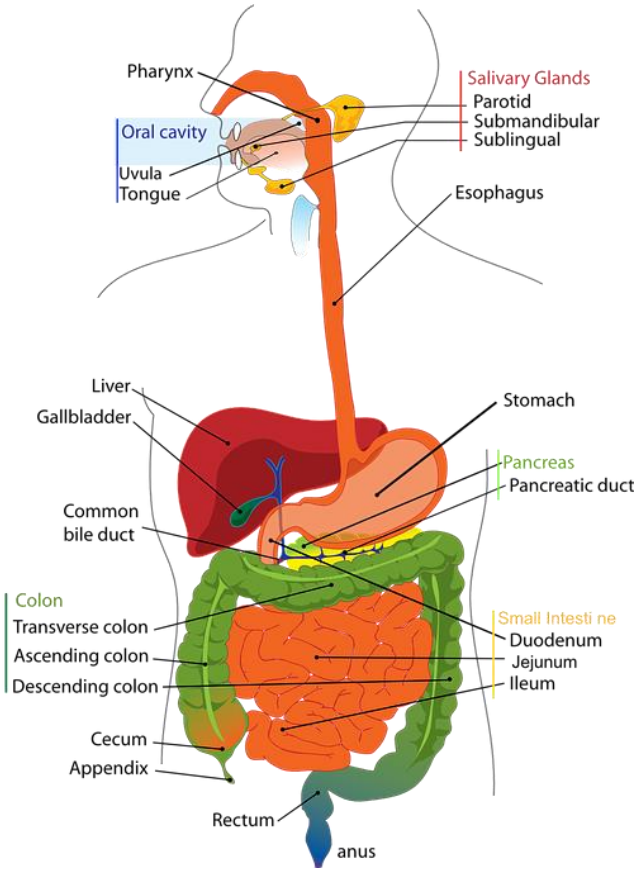


Figure 2.1.1- *The organs of the gastrointestinal system, reprinted with permission from Pixabay*

2.1.2 Function of the gastrointestinal system

The functions of the GI tract are carried out by specific actions of each organ. For instance, both mechanical and chemical breakdown of food occurs throughout the GI tract, from the chewing food in the mouth and the release of stomach acid, for example. This acidic environment of the stomach stimulates protein digestion. Food is transported along the GI tract by muscles lining the tract from oesophagus to rectum performing co-ordinated contractions called peristalsis (Greenwood-Van Meerveld, Johnson, & Grundy, 2017).

Absorption of nutrients, including amino acids and sugars, from broken-down food occurs in the small bowel. Key vitamins absorbed in the small bowel include folate and Vitamin B12 (Kozyraki & Cases, 2013). The small bowel, approximately 24 feet, consists of the duodenum, jejunum and ileum. The colon is subdivided into caecum, ascending colon, transverse colon, descending colon and rectum. The main action of the large bowel is the absorption of water as well as certain vitamins (Vitamin K and B1). Faeces is solid when it enters the sigmoid colon and it is then stored in the rectum- the last 8 inches of the large bowel, until it is excreted through the anus by voluntary relaxation of the anal sphincters (Reed & Wickham, 2009).

Salivary glands aid digestion by releasing chemicals that initiate digestion of food, particularly starch by the amylase enzyme. The liver produces bile that is stored in the gallbladder, which aids the absorption of fat molecules in the small intestine. Bile is reabsorbed in the terminal ileum or excreted out of the body in faeces (Camilleri, 2014). Detoxification of absorbed products of digestion is another important function of the liver (Reed & Wickham, 2009). The role of the pancreas in digestion is twofold, firstly- the release of pancreatic enzymes initiates digestion of food within the small bowel, and secondly the release of hormones such as insulin and glucagon maintain homeostasis of blood glucose (Rehfeld, Nylander, & Karnov, 2017)

2.2 Epidemiology of inflammatory bowel disease

Geographically, the highest incidence rates of IBD arise from Northern Europe and North America. In 2010, total incidence rates in Western Europe were 6.3 for Crohn's Disease (CD) and 9.8 for Ulcerative Colitis (UC) per 100,000 person-years. These rates were lower in Eastern Europe, 3.3 and 4.6 per 100,000 respectively (Burisch, 2014). In Northern Europe, the United Kingdom and Scandinavia have the highest incidence of IBD. There are approximately 620,000 people living with IBD in the UK (Mikocka-Walus, Power, Rook & Robins, 2018). These regions have consistently had

higher rates of IBD whereas places like Latin America, Eastern Europe and Asia have been considered to be less affected (Burisch *et al*., 2013). However, there has been an increase in IBD, particularly UC, in these areas over recent years. Potential explanations for this include a move towards a more industrialised and 'Westernised' society in these regions, as well as improved identification of the disease (Loftus, 2004).

People with IBD are mostly diagnosed between the ages of 20 to 30 years old, although both the paediatric and older population can be affected (Duricova *et al*., 2014). It is estimated that, of those with IBD, between 10-15% are diagnosed under 18 years of age (Heyman *et al*., 2005) This demonstrates a considerable disease burden amongst the younger population.

2.3 Crohn's disease

CD typically causes non-continuous areas of inflammation anywhere along the GI tract from mouth to anus, **Figure 2.3.1(a)**. These discrete areas of disease are known as 'skip lesions', as healthy bowel is punctuated by sections of inflammation. CD commonly affects the union of the small and large bowel, called the terminal ileum and often spares the rectum. At colonoscopy, typical appearances include 'cobblestoning' appearance may be identified, **Figure 2.3.1(b)**. When microscopically examining biopsies, inflammation affects all layers of the bowel wall and discrete granulomas may be seen (Mas-Moya & Singhi, 2015). Granulomas form when various immune cells cluster together and may be present in other infective or inflammatory conditions. However, when present in the biopsy of individuals experiencing IBD-like symptoms, they confirm the diagnosis of CD (Molnár, Tiszlavicz, Gyulai, Nagy, & Lonovics, 2005). These colonoscopic and histologic features help to differentiate between CD and UC.

The prototypical symptoms and signs of CD include weight loss, diarrhoea and abdominal pain alongside fever, fatigue and poor appetite (Ghosh & Mitchell, 2007; Mowat *et al*., 2011). Certain

complications may occur with CD, either before or after diagnosis. Perianal fistulae are abnormal connections between two organs that are usually separate and are commonly associated with CD (Kotze *et al.*, 2018). For 10% of people, perianal fistula is the first manifestation. Perianal fistulae typically occur from the rectum or anus to the perianal skin, from rectum to vagina called a rectovaginal fistula or from the rectum to the bladder, a colovesical fistula. Symptoms may include pain, discharge, impaired sexual function, gas in the urine stream or passing gas per vagina, depending on the type of fistula (Kotze *et al*., 2018).

Strictures may occur in the GI tract which result from ongoing inflammation leading to fibrosis. This inflammation and fibrosis disrupts the normal anatomy of the bowel wall and leads to destruction of the muscular layers (Chang *et al*., 2015). Intestinal adhesions are another complication and arise when fibrosis connects intra-abdominal organs to each other or to the intra-abdominal wall. General symptoms include bloating, abdominal pain and nausea (Tabibian, Swehli, Boyd, Umbreen, & Tabibian, 2017). Both strictures and adhesions may lead to bowel obstruction or perforation. In this context, patients may present acutely with signs and symptoms consistent with intestinal obstruction or bowel perforation and may require urgent surgery. Such symptoms include severe abdominal pain, constipation and vomiting, which may contain faecal matter (Hwang & Varma, 2008; Mas-Moya & Singhi, 2015). As described in section 2.1.2, a number of vitamins are absorbed in the terminal ileum, therefore inflammation due to CD in this area can result in vitamin deficiencies. Similarly, reduced reabsorption of bile acids by the small bowel, referred to as bile acid malabsorption, can lead to a plethora of issues including steatorrhoea (diarrhoea caused by increased concentrations of fat within stool), pigment gallstones and kidney stones, **Table 2.4.1** (Lenicek et al., 2011; Vítek, 2014). Regarding Extra-intestinal manifestations (EIM), arthritis, erythema nodosum and ankylosing spondyloarthritis are largely associated with CD (Vavricka *et al*., 2015; Yi *et al.*, 2012) . Further information on EIM can be found in section 2.6.

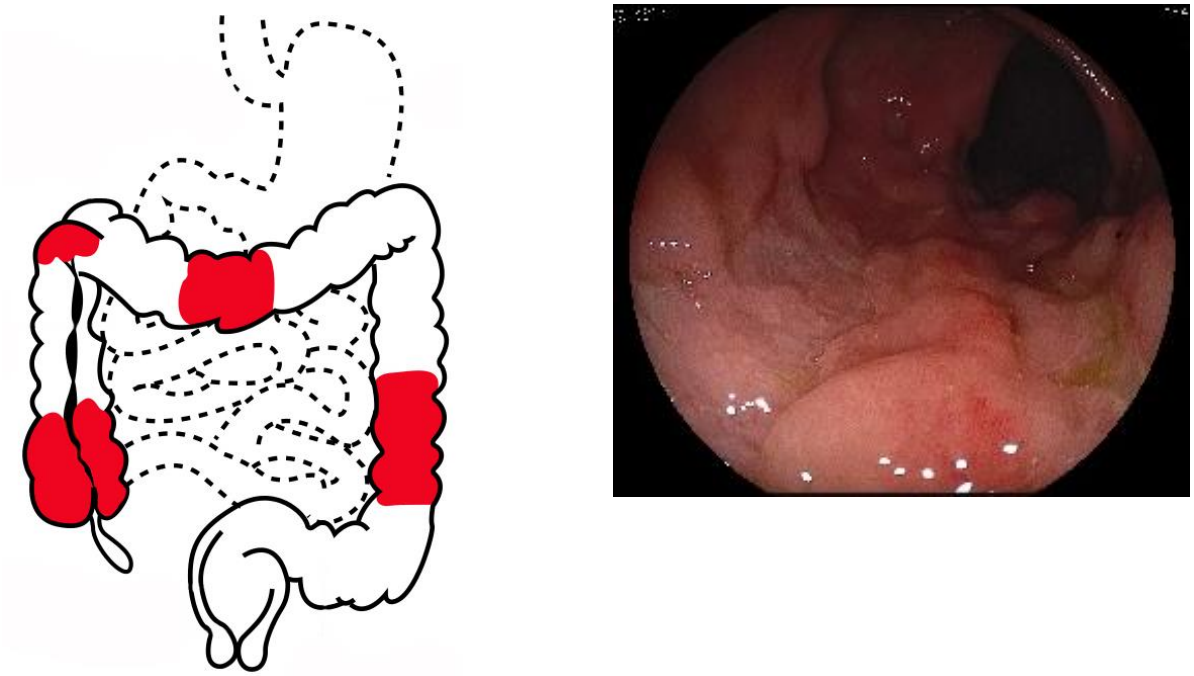


Figure 2.3.1- *The disease distribution of CD within the GI tract, highlighted in red (a), endoscopic features of CD (b) reprinted with permission from Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Crohn%27s_Disease_vs._Ulcerative_Colitis.jpg) and the European Crohn's and Colitis Organisation*

2.4 Ulcerative colitis

UC affects the large bowel, causing continuous and uniform inflammation that originates in the rectum and progresses through the large bowel, see **Figure 2.4.1(a)**. Although UC is a disease confined to the large bowel, 'backwash ileitis' can occur from profound inflammation that extends into the small bowel. Circumferential and superficial ulceration with friable blood vessels are typical findings of UC during colonoscopy, as seen in Figure **2.4.1(b)**. Histologically, UC causes ulcerative inflammation that does not affect all layers of the bowel wall (Mowat et al., 2011).

Rectal bleeding and diarrhoea are the key symptoms of UC (Ghosh & Mitchell, 2007). Patients may also describe urgency and a feeling of incomplete evacuation of stool, known as tenesmus (Mowat et al., 2011). The EIM associated with UC are pyoderma gangrenosum and primary sclerosing cholangitis (Vavricka et al., 2015). Complications include acute-severe, or fulminant, UC which is

characterised by worsening rectal bleeding, diarrhoea, fever and abnormal blood results, such as elevated CRP and ESR. The Truelove-Witts criteria is used to identify these acute episodes and treatment initially involves intravenous rehydration and corticosteroids, although proctocolectomy may be indicated in severe colitis which is unresponsive to medical management (Lasch et al., 2016). Diagnosis and management of acute-severe UC are discussed in sections 2.8.5 and 2.10.2 respectively. Toxic megacolon is a rare but potentially life-threatening complication. It can be caused by pseudomembranous colitis (infectious colitis caused by *Clostridium difficile* infection), ischaemia and UC, although CD patients with ileocolic disease may be at increased risk. It is characterised by dilation of the large bowel due to deep inflammation which weakens the contractility of the muscles in the bowel wall **(Table 2.4.1)** (Autenrieth & Baumgart, 2012). The management of toxic megacolon is discussed under surgical management of IBD in Section 2.11.2.

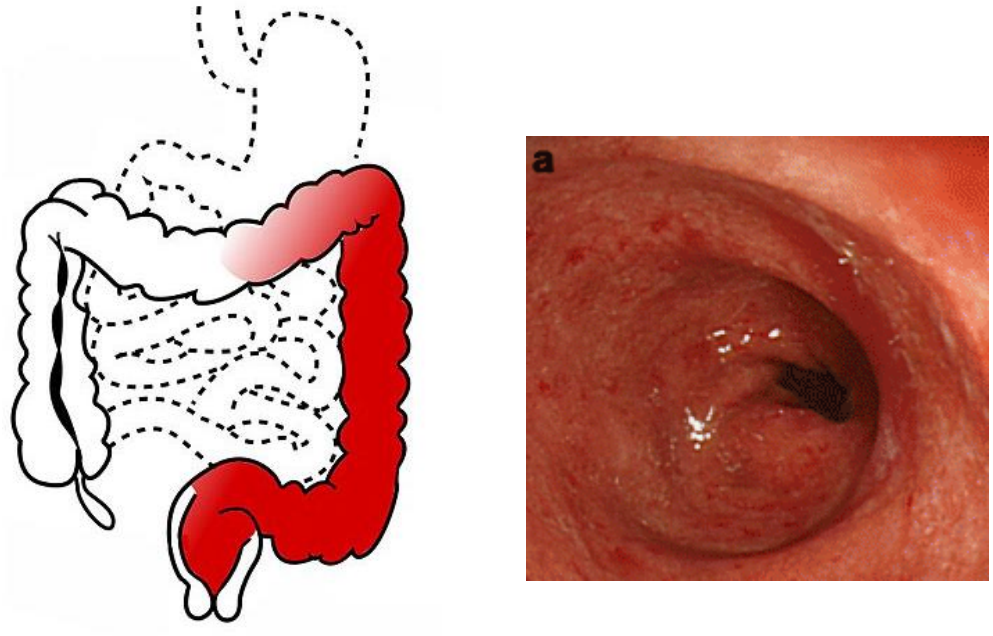


Figure 2.4.1*- disease distribution of UC, highlighted in red (a), endoscopic features of UC (b), reprinted from Gastroenterology Consultants of Augusta and 'Endoscopic approach in ulcerative colitis', reprinted with permission from Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Crohn%27s_Disease_vs._Ulcerative_Colitis.jpg) and* Yamada et al., 2018; BMC Gastroenterology

Table 2.4.1- The key differences between Crohn's Disease and Ulcerative Colitis

	CD	UC
Key symptoms	Diarrhoea, abdominal pain, perianal disease, weight loss	Rectal bleeding, tenesmus, abdominal pain, bloating
Location of disease	Mouth to anus, discontinuous areas of inflammation	Large bowel only, with potential for 'backwash ileitis'
Diagnostic findings	Macroscopic- cobblestone Microscopic- granulomas	Macroscopic- continuous ulceration Microscopic- ulceration, friable vessels
Complications	Bowel stenosis, adhesions → obstruction Abscess, perianal disease, bile acid malabsorption	Dilation of large bowel → toxic megacolon

2.5 Indeterminate colitis

In approximately 10% of patients in whom a diagnosis of IBD has been confirmed, a diagnosis of CD or UC cannot be made based on standard investigations like endoscopy or histology. Such people are diagnosed with Indeterminate Colitis (IC) or IBD-unclassified. This group of individuals is poorly-defined, as a certain proportion are later diagnosed with either UC or CD though many will remain IC. There is currently no diagnostic test that will confirm a diagnosis of IC and it is considered a diagnosis of exclusion, as a diagnosing IC is based upon ruling out other conditions like CD or UC. IC patients tend to be managed similarly to UC patients; however for those who undergo a colectomy, they have an increased risk of complications than UC patients, but less than CD patients (Tremaine, 2011).

2.6 Extra-intestinal manifestations

EIM are signs and symptoms of IBD that are external to the GI tract. Approximately 25-40% of patients display EIM as part of their CD or UC (Levine & Burakoff, 2011). The most common system

affected by EIM is the musculoskeletal system, where arthritis can occur in the sacroiliac joints, spine and peripheral joints, frequently referred to as IBD related arthropathy. Osteoporosis can also arise due to steroid use, intestinal malabsorption and inflammatory-mediated bony destruction and can increase the risk of fracture (Targownik, Bernstein, & Leslie, 2013). A variety of skin manifestations are also associated with IBD, of which erythema nodosum and pyoderma gangrenosum are key examples. Erythema nodosum is the most common, presenting as deep, tender lesions often overlying the shins due to inflammation in subcutaneous fat. Pyoderma gangrenosum begins as a pustule or papule which breaks down into an ulcer, often coated with pus or necrotic debris (Levine & Burakoff, 2011).

The hepatobillary system can also be affected in IBD. For example, primary sclerosing cholangitis is particularly associated with UC and causes stricturing of the bile ducts, which transport bile from the liver into the gallbladder for storage or into the small intestine via the pancreas. It may be asymptomatic, identified only through abnormal liver function blood tests, though patients may present with jaundice. Primary sclerosing cholangitis is an independent risk factor for cholangiocarcinoma, which is cancer of the biliary system, or colorectal cancer (Karlsen, Folseraas, Thorburn, & Vesterhus, 2017; Levine & Burakoff, 2011). Ocular symptoms occur in 0.3 to 5% of all IBD patients, often in association with peripheral arthritis and erythema nodosum. Conditions include episcleritis, causing redness, irritation and burning and scleritis, which can impair vision as well as causing redness and pain. Often, the severity of EIMs mirrors the severity of the IBD and the mainstay of most treatment is to reduce IBD disease activity (Levine & Burakoff, 2011). **Table 2.6.1** provides an overview of the EIMs of IBD.

Table 2.6.1- The extra-intestinal manifestations of inflammatory bowel disease

Body system	Extra-Intestinal Manifestation
Musculoskeletal	Arthritis (spine, sacroiliac joints, peripheral joints), ankylosing spondylitis, tendonitis, clubbing, osteoporosis, fracture
Skin	Erythema nodosum, pyoderma gangrenosum, psoriasis, aphthous stomatitis, Sweet syndrome, metastatic CD
Hepatopancreatobiliary	Primary sclerosing cholangitis, pigment gallstones
Eye	Episcleritis, scleritis, uveitis
Renal	Renal stones, obstructive uropathy, urinary fistulae

2.7 Aetiology of inflammatory bowel disease

Many risk factors have been linked to IBD, though the causes are incompletely understood. The general consensus is that genetically susceptible individuals are affected by as-yet unconfirmed environmental exposures. This section discusses the proposed explanations behind IBD.

2.7.1 Genetic risk

A link between genetics and IBD has been demonstrated. For instance, monozygotic twin studies have demonstrated concordance rates of 10-15% in UC and 30-35% in CD (Khor *et al*., 2011). However, genetics have also been implicated in UC through a systematic review carried out by Childers *et al*. (2014). They found that UC patients diagnosed before the age of eighteen had a stronger family history of IBD than those diagnosed after eighteen and they were likely to be

diagnosed at a younger age than their affected family members were when they were diagnosed (Childers *et al*., 2014).

The CARD 15 gene, which codes for the NOD2 immune receptor, was the first gene identified in the development of CD in the white population. NOD2 receptors are found within cells and their function is to maintain homeostasis between intestinal bacteria and the intestinal wall by stimulating Paneth cells, a type of immune cell, to release proteins, called alpha-defensins, as an innate immune response (Baumgart & Carding, 2007). Mutations in the CARD15 gene causes a reduction in NOD2 receptors which leads to the release of pro-inflammatory cytokines which are chemicals that generate an immune response which damages the intestinal lining (Yamamoto-Furusho *et al.*, 2018).

The Genome-Wide Association Studies (GWAS) have identified 99 genetic risk loci for IBD, including 28 genes associated with both CD and UC. GWAS has identified genetic variations which alter certain immune signalling chemicals and pathways that lead to the inflammation of IBD, including JAK2 and IL-10 (Khor *et al*., 2011; Verstockt, Smith, & Lee, 2018).

2.7.2 Tobacco smoking

Cigarette smoking is a known risk factor for CD, with ex-smokers also at increased risk (Lunney *et al*., 2012). Surprisingly, smoking has been shown to be protective for the development of UC, with people developing UC typically being non- or ex- smokers. Additionally, smokers who do develop UC are more likely to display milder disease than their non-smoking counterparts (Lunney *et al.*, 2012). The mechanism by which smoking or nicotine confers protection in UC is unknown, but has been linked to changes in inflammatory and immune signalling, permeability of the GI tract and blood vessels. In light of the apparent differences smoking has on UC and CD, it is unlikely to be

caused by immune changes alone as if this were the case, both CD and UC should improve following smoking (Thomas, Rhodes, Green, & Richardson, 2000).

2.7.3 Diet and lifestyle

As IBD has consistently affected Western countries, a link between the Western diet and IBD has been proposed. Evidence supporting this includes a systematic review undertaken by Forbes *et al*., which identified literature citing a connection between diet and IBD. For instance, there appears to be an increased risk of developing CD with increased consumption of saturated fats and meat. UC has been linked to poly-unsaturated fatty acids, omega-6 fatty acids and meat. A diet high in fibre and fruit appears to decrease the risk of CD, but not UC (Forbes *et al*., 2017). Khalili *et al*. propose that a diet high in sugar and unsaturated fats may cause abnormalities in the microbes of the GI tract and alter the barrier function which could contribute to IBD (Khalili *et al*., 2018).

An association between improved hygiene standards since 1980 and CD has been postulated, for example access to clean water and smaller family sizes causing a reduction in overcrowding. This decreased exposure to microbes, like bacteria, during childhood may impede the development of the immune system, causing an excessive immune response at times of microbe exposure. This is known as the 'hygiene hypothesis' and has been linked to many autoimmune and allergic diseases such as IBD and asthma (Castiglione *et al*., 2012; Stiemsma *et al*., 2015).

2.7.4 Additional risk and protective factors

Other proposed risk factors for IBD include GI infections, not being breastfeed, oral contraceptive pill and antibiotic use, but evidence around these factors remains limited (Loftus, 2004; Ponder & Long, 2013).

Undergoing an appendectomy has been found to confer some protection against the development of UC (Loftus, 2004).

2.8 Diagnosis of inflammatory bowel disease

2.8.1 History

In patients presenting with certain GI symptoms, such as diarrhoea, tenesmus, weight loss, rectal bleeding and nocturnal defaecation, IBD is an important differential diagnosis. Assessing the cause of any symptoms involves taking a comprehensive history from the patient, performing an appropriate examination and arranging appropriate investigations. The patient history should explore symptoms, family history, recent travel history and affected contacts to predict an infective, endocrine or autoimmune origin to symptoms. A typical history of possible IBD may involve symptoms of diarrhoea, rectal bleeding and weight loss for many weeks (Abreu & Harpaz, 2007).

2.8.2 Clinical examination

A thorough examination should be performed, including a general assessment of health to identify possibly signs of anaemia or the EIM of IBD. Examining the oral cavity, abdomen and perineum should be done as part of the examination of the GI system (Abreu & Harpaz, 2007). Angular stomatitis (erythema and maceration of the skin adjacent to the angle of the mouth), perianal disease and any abdominal pain or mass may indicate IBD. Perianal complications are present in over 50% of Crohn's disease patients, therefore the perineum should be inspected and a digital rectal examination should be performed to identify pain and blood or pus on the glove. As 40% of

IBD patients have EIMs including uveitis and erythema nodosum, examination of eyes, skin and musculoskeletal system should be performed (Huang, Chandra, & Shih, 2012; Harper *et al.*, 1987).

2.8.3 Initial investigations

Many investigations are used in combination to diagnose IBD. Though colonoscopy and biopsy are used to confirm the diagnosis of IBD, other investigations should be performed to identify patients with features suggestive of IBD before they undergo this invasive test. Routine blood tests should be performed in primary care, including a Full Blood Count to identify anaemia and elevated white blood cells, which suggests infection or inflammation (Bochner, 2000). Markers of inflammation like C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and ferritin should be tested for. In addition to being an acute phase protein indicative of inflammation, ferritin levels also identify anaemia, which is common in IBD due to reduced uptake of iron within the duodenum and jejunum and GI bleeding (Schmidt *et al*., 2016). A screening test to exclude Coeliac disease should also be performed. Stool culture and microscopy with *Clostridium difficile* toxin assay can identify an infective cause of symptoms (Abreu & Harpaz, 2007).

Although CRP and ESR are important tests to identify inflammation, the faecal calprotectin level identifies inflammation specifically within the GI tract. Calprotectin is a protein found within white bloods cells called neutrophils, which infiltrate the gastrointestinal tract during inflammatory conditions like IBD and are passed in faeces where concentrations can be measured (Banerjee et al., 2015). Therefore, a normal faecal calprotectin level excludes IBD as GI inflammation is absent (Carter, Lobo, & Travis, 2004). Consequently, the National Institute of Health and Care Excellence (NICE) recommends the use for faecal calprotectin in patients to differentiate between inflammatory and non-inflammatory causes of symptoms, in both a primary and secondary care

setting (NICE, 2013). This test was first introduced for use by UK gastroenterologists in 2013 and has since been available in primary care.

2.8.4 Secondary care referral

A suspected diagnosis of IBD should result in a referral to appropriate secondary care services, either an adult or paediatric consultant gastroenterologists where a macroscopic and histological diagnosis can be made through sigmoidoscopy or colonoscopy and biopsy (NICE 2015). Specialists may perform or repeat investigations done in primary care. Patients under NHS healthcare may be referred to secondary care under different pathways. For instance, in suspected IBD patients should have a specialist appointment within four weeks. Alternatively, patients may fulfil the criteria for the two-week wait referral (NICE, 2015). This referral system was first introduced in 2000 and guides primary care to urgently refer patients displaying certain criteria, like being 40 years and over with abdominal pain and weight-loss or 60 years and above with iron deficiency anaemia, as colorectal cancer must be ruled out (NICE 2015). As there is overlap with the symptoms of IBD and those of cancer, it is possible that some individuals are diagnosed via this referral pathway.

In order to assess the extent of disease in IBD, the boundaries of inflammation should be identified by an endoscopic procedure like oesophagogastroscopy, sigmoidoscopy or colonoscopy. Endoscopy involves the introduction of a thin tube into the GI tract, either via the mouth or anus, which has a camera on the end to allow the operator to observe the inner layer of the GI tract. Biopsies can be taken by inserting biopsy forceps through the endoscope to sample the tissue. Sigmoidoscopy is a useful investigative procedure for UC; however there is a risk of missing a diagnosis of CD as there may be further inflammation beyond the limit of the sigmoidoscope (Langan, Gotsch, Krafczyk, & Skillinge, 2007). As such, a colonoscopy may be performed which can diagnose both UC and CD.

Proctoscopy is a procedure which can be performed in an outpatient appointment, though it only offers a limited view of the anus and rectum. CD affecting the upper GI tract can be seen on oesophagogastroscopy. **Figure 2.7** outlines the sections of bowel that can be observed using different endoscopic techniques.

Additional imaging may be required to identify small bowel or ileocolonic CD, such as an MRI scan of the abdomen or wireless capsule endoscopy (a swallowed video capsule). Perianal disease can be assessed by MRI scan. A laparoscopic approach to diagnosis may be required, albeit it very rarely, especially when there is a possibility of intestinal tuberculosis, which as previously discussed is particularly relevant in areas of the world where tuberculosis is endemic (Mowat et al., 2011).

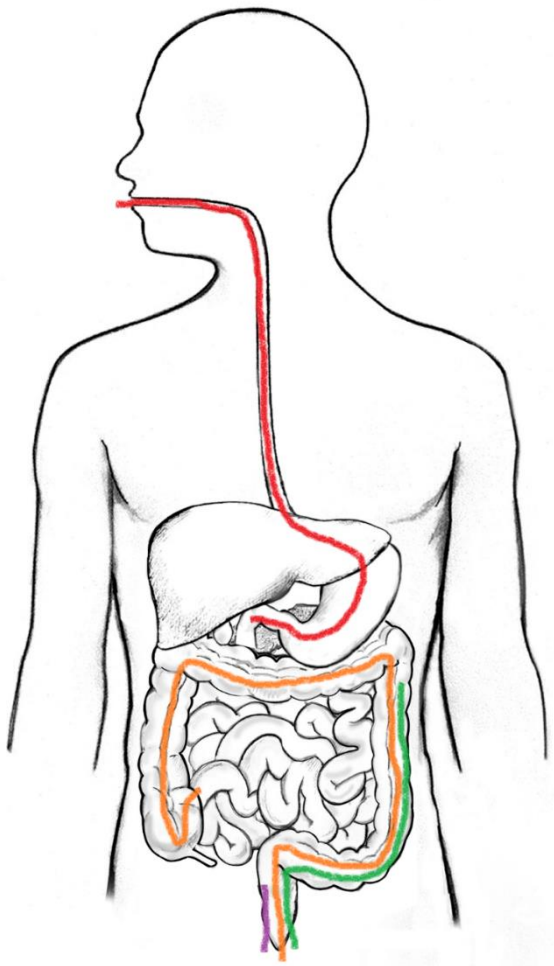


Figure 2.8.1- *The endoscopic procedures used to diagnose IBD: oesophagogastroscopy (red), colonoscopy (orange), sigmoidoscopy (green) and proctoscopy (purple), reprinted with permission from National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health*

2.9 Diagnostic criteria for inflammatory bowel disease

As outlined in Section 2.8.3, there are a wide range of investigations that can be carried out to determine the presence of IBD but there is no gold-standard test. Consequently, clinicians use clinical presentation, endoscopic and histological findings to diagnose IBD, which have been collated within criteria that can be used to aid the diagnosis of IBD.

The Lennard-Jones criteria is the most well-known criteria used to diagnose CD. It focuses on the histological appearance of colonic biopsies, splitting the characteristics of CD into 'major' (granuloma) and 'minor' (fibrosis, macroscopic discontinuation of disease, transmural inflammation) items. A confirmed or probable diagnosis of CD is made by the presence or absence of these items, seen in **Table 2.9.1** (Reinisch *et al*., 2016).

Table 2.9.1- *The Lennard-Jones criteria, adapted from Reinisch (2016)*

	Lennard-Jones Criteria
Major Item	Granuloma (aggregation of immune cells)
Minor Item	Transmural inflammation (inflammation spanning all layers of the bowel wall) Macroscopic discontinuity of disease ('skip lesions') Fibrosis (damaged bowel wall from chronic inflammation) Lymphoid aggregates (collection of white blood cells) Discontinuous inflammation on histology
'Established CD' **'Probable CD'** **'Non-CD'**	1 major + 1 minor/ 3 minor 2 minor 1 major/ 1 minor / none

The European Crohn's and Colitis Organisation (ECCO) have generated some guidelines for diagnosing IBD. These guidelines acknowledge that a single reference standard does not exist for CD or UC and recommends factors that clinicians should consider when diagnosing individuals with IBD, including the patient's presenting symptoms as well as the results of any investigations. The criteria for diagnosis is based on clinical presentation, endoscopic, cross-sectional imaging,

histological and biochemical investigations, which is also reflected within current NICE guidelines (Maaser *et al*., 2018; NICE 2015). Examples of the guidance included aid the clinician to consider other diagnoses and select the most appropriate investigations to confirm or refute IBD. For example, in order to exclude GI infections, symptoms should be present for over six weeks and stool specimens should be obtained. Regarding colonoscopic diagnosis, ileocolonoscopies with biopsies of inflamed tissue from at least two locations in the colon should be completed; continuous inflammation with rectal involvement may indicate UC whereas CD should be suspected when discontinuous lesions, strictures and fistulae are present. The endoscopic and histologic differences between CD and UC can be found in **Table 2.4.1**.

Research has been carried out that compares the clinical efficacy of the Lennard-Jones and ECCO criteria. This study, conducted by Reinisch *et al*. found that there are limitations with the Lennard-Jones criteria, as when it was applied to 328 patients with long-standing, confirmed CD who had been diagnosed with the ECCO criteria, 49% (n= 162) would not have been identified as having CD at the time of their diagnosis, demonstrating some weaknesses in this diagnostic criteria (Reinisch *et al.*, 2016).

There are also criteria that can assess the severity of IBD once diagnosed. For example, the Truelove and Witts Severity Index for UC uses characteristics like stool frequency per day and blood in stool alongside the presence of fever, anaemia and raised ESR to determine disease severity (**Table 2.9.2**) (Sehgal & Koltun, 2010). Similarly, the Montreal classification measures the behaviour of the disease, for example, stricturing disease, which is the narrowing or stenosis of the bowel; or penetrating disease, where perforations have occurred; and location along the GI tract (**Table 2.9.3**) (Sehgal & Koltun, 2010). The Mayo score is another means of assessing the severity of UC, combining disease severity with endoscopic findings and the physician's global assessment (**Table 2.9.4**). Disease severity is established by stool frequency and the presence or absence of rectal

bleeding. Within each category, a maximum of three points can be scored. A higher score indicates increased severity (Paine, 2014; Schroeder, Tremaine, & Ilstrup, 1987).

Table 2.9.2- *The Truelove Witts criteria, used to assess disease severity of UC, adapted from* Kedia, Ahuja and Tandon (2014)

	Mild	**Moderate**	**Severe**
Number of bloody stools per day	<4	4 - 6	>6
Pulse	<90 bpm	≤90 bpm	>90 bpm
Temperature	<37.5°C	≤37.8°C	>37.8°C
Haemaglobin	>11.5g/dL	≥10.5g/dL	<10.5g/dL
ESR	<20mm/h	≤30mm/h	>30mm/h
CRP	Normal	≤30mg/dL	>30mg/dL

Key: ESR; Erythrocyte Sedimentation Rate, CRP; C-Reactive Protein, bpm; beats per minute, g; gram, dL; decilitre, mm; millimetre, h; hour.

Table 2.9.3- *The Montreal Classification, used to assess the severity of both CD and UC, adapted from Satsangi, Silverberg, Vermeire and Colombel (2006)*

	Montreal Classification
Crohn's Disease	
Age of diagnosis	A1- <16 yrs A2- 17 – 40 yrs A3- >40 yrs
Location	L1- ileal L2- colonic L3- ileocolonic L4- isolated upper disease
Behaviour	B1- non-stricturing/non-penetrating B2- stricturing B3- penetrating P- perianal disease
Ulcerative Colitis	
Extent	E1- ulcerative proctitis (distal to rectosigmoid junction) E2- left-sided UC (distal to splenic flexure) E3- extensive UC (proximal to splenic flexure)
Severity	S0- clinical remission/asymptomatic

Table 2.9.4- *The Mayo Score, used to assess disease severity of UC, adapted from Tremaine and Ilstrup (1987)*

Stool frequency	0- Normal number for this patient 1- 1 to 2 more than normal 2- 3 to 4 more stools than normal 3- 5 more stools than normal
Rectal bleeding	0- No blood seen 1- Streaks of blood with stool less than half the time 2- Obvious blood with stool most of the time 3- Blood alone passes
Findings on endoscopy	0- Normal/inactive disease 1- Mild disease (erythema, decreased vascular pattern, mild friability) 2- Moderate disease (marked erythema, lack of vascular pattern, friability, erosion) 3- Severe (spontaneous bleeding, ulcerations)
Physician's global assessment	0- Normal 1- Mild disease 2- Moderate disease 3- Severe disease

2.10 Differential diagnoses of inflammatory bowel disease

There are certain conditions that must be considered by the clinician when faced with a patient describing similar GI symptoms to those discussed previously. Through examination and careful selection of investigative tests, the correct diagnosis may be established. The following conditions are some of the differential diagnoses of IBD.

Irritable bowel syndrome (IBS) is a common functional condition affecting the GI tract. It is characterised by abdominal pain and bloating, alongside a change in frequency and form of bowel habit. Whilst not fully established, IBS has been linked to a disorder of the brain-gut communication between the central nervous system and nervous system of the GI tract, called the enteric nervous system. The diagnosis is largely symptom-focussed. Management involves

alleviating symptoms through dietary modification, antispasmodics and other pharmacological management for diarrhoea or constipation. IBS differs from IBD in that patients frequently experience relief in their symptoms after defaecation and they would have normal colonoscopic findings and faecal calprotectin levels (Weaver *et al*., 2017).

The symptoms and signs of IBD also overlap with colorectal cancer, including rectal bleeding, weight loss, abdominal mass and anaemia. Patients with CD or colorectal cancer can develop strictures. As clinical presentation is similar, differentiating IBD from colorectal cancer involves endoscopic and histological assessment of the bowel, as anaemia and elevated CRP may be present in cancer and IBD (Holm et al., 2018). A tumour may be visible by endoscopy and a biopsy would reveal cancerous cells (Hamilton, Round, Sharp, & Peters, 2005). Colorectal cancer is more prevalent in the older population, meaning increased vigilance is needed in older people presenting with these symptoms to identify the cause (Ahnen et al., 2014).

As the GI tract is in contact with the external environment, there is potential for infection. In the developed world, viruses are mostly responsible for gastroenteritis, with bacteria contributing to a small proportion of gastroenteritis (Oude Munnink & van der Hoek, 2016). Common viral causes of gastroenteritis include norovirus and rotavirus, whilst *Salmonella*, *Campylobacter* and *Shigella* are bacterial causes (Oude Munnink & van der Hoek, 2016; Singh et al., 2015). Gastroenteritis leads to diarrhoea, vomiting, fever and abdominal pain. Generally, these symptoms are acute-onset and resolve over a few days; however, microbes such as *Giardia lamblia* can cause protracted symptoms. Diagnosis is achieved by conducting a food and travel history and arranging blood tests and stool culture if symptoms persist. Management involves rehydration and, rarely, antibiotics (Al Jassas et al., 2018). Gastroenteritis differs from IBD in the length of symptoms, as it is an acute condition that tends to resolve quickly and with no further complication. On the other hand, symptoms of IBD are more chronic with episodes of worsening of symptoms, or ‘flares’.

Nevertheless, following an episode of gastroenteritis, symptoms can outlast the initial infectious insult resulting in post-infectious irritable bowel syndrome (Gwee, 2010).

Diverticular disease is another differential diagnosis and is more common in the older population. It is thought that up to 50% of individuals have colonic diverticula, which are small outpouchings of the colon. It is thought to arise from high pressures within the bowel from constipation and small stool volumes. Diverticular disease can be asymptomatic, though rectal bleeding, abdominal pain and fever may occur due to diverticulitis (Weizman & Nguyen, 2011). Complications include rectal haemorrhage, abscess formation or the development of fistulae which is similar to complications of IBD. Increasing dietary fibre is the mainstay of treatment, alongside oral antibiotics or intravenous treatment in uncomplicated or complicated diverticulitis (Weizman & Nguyen, 2011) In older people with this clinical presentation, diverticular disease would be most common, although IBD is an important differential to exclude.

Haemorrhoids are a common condition affecting the anorectal region of the GI tract. They arise from venous dilation following deterioration of the supportive network in anal cushions, which has been linked to constipation, straining and pregnancy. Painless rectal bleeding is the most common manifestation, with perianal itching occurring due to prolapsed haemorrhoids. Diagnosis is clinical and management consists of dietary changes or surgical intervention (Lohsiriwat, 2012). IBD may be misdiagnosed as haemorrhoids due to rectal bleeding. However, if a patient presents with multiple GI symptoms, an alternative diagnosis should be considered.

2.11 Management of inflammatory bowel disease

Managing IBD requires expert multidisciplinary team involvement to educate and support patients. Depending on the clinical need of the patient, gastroenterologists, colorectal surgeons, hepatologists, dieticians and physiotherapists may be involved in their care (Ricci, Lanzarotto, &

Lanzini, 2008). The IBD patient must be considered holistically, including the impact of the condition on nutrition, growth and mental wellbeing. Treatment options differ depending on the extent of disease and whether the patient is in remission or has active inflammation (Bernstein, 2015).

All patients diagnosed with IBD in the UK should be cared for by a specialist IBD team (Lee & Melmed, 2017). This should comprise of a named gastroenterologist, IBD nurse specialists, colorectal surgeons, pathologist and dietician. Patients are able to contact their team with any issues, for example relapsing symptoms and hospital admissions. This ensures continuity of care and allows prompt management of flares. As previously described in section 2.3, IBD can cause weight loss and CD in particularly is associated with nutrient deficiency, so dietetic care is important. As part of their treatment, patients with IBD are able to access a range of specialist services, including rheumatology, dermatology, ophthalmology and psychology (Mowat et al., 2011).

2.11.1 Medical management

The aim of medical management of IBD is to weaken the aberrant immune and inflammatory responses occurring in the GI tract. There are different management options for active disease, commonly known as a 'flare', or to maintain remission (Bernstein, 2015). If the patient is experiencing a flare, corticosteroids and thiopurines may be used to induce remission. Steroids are not used to maintain remission due to the wealth of adverse effects they may cause, including weight gain, diabetes, hypertension and osteoporosis (Waljee et al., 2017). Instead, aminosalicylates, thiopurines and anti-Tumour Necrosis Factor Alpha (TNFα) therapy can be used. Anti-TNFα therapy, also known as 'biological therapy', has been shown to reduce inflammation and promote healing of damaged bowel. Side effects of the immunosuppressive agents to treat IBD

include fever and an increased risk of infections, including TB (Mowat et al., 2011). Medical treatment of perianal disease involves the use of thiopurines, biological therapy and antibiotics, commonly metronidazole and ciprofloxacin (Klag, Goetz, Stange, & Wehkamp, 2015). There is a role for antibiotics in the management of IBD. The use of probiotic therapy is also being explored, though evidence of any clinical effectiveness is largely inconclusive (Guandalini & Sansotta, 2019). A further novel procedure in the management of IBD is faecal microbiota transplantation. However, a systematic review conducted by Colman and Rubin containing eighteen included papers found variable results and more research is needed in this field (Colman & Rubin, 2014). Complications of IBD may also require management, including iron replacement therapy by using oral ferrous sulphate, ferrous fumarate or intravenous iron, although side effects may include GI intolerance with oral tablets and intravenous treatment can be costly and inconvenient for patients. Oral ferric maltol may be a useful alternative, as a placebo-controlled trial demonstrated improvements in haemoglobin as well as being well-tolerated by participants (Schmidt et al., 2016). Additional complications of IBD which may require treatment include vitamin deficiencies which may require intramuscular injections and bile salt malabsorption, which can be managed using colesevelam hydrochloride (NICE, 2013).

2.11.2 Surgical management

A significant role for the surgical management of IBD exists, both in elective and urgent scenarios. For CD, surgical intervention involves resecting diseased bowel and is reserved for failed medical management, stricturing or fistulating disease and perforation. The same patient may require multiple resections due to recurrence of the disease in another area of bowel and it is difficult to predict individuals at increased risk of this (Hwang & Varma, 2008). For instance, in a population-based retrospective cohort study of 1936 patients with CD, the cumulative rate of intestinal re-resection was 33% at 5 years and 44% at 10 years after the initial resection (Bernell, Lapidus, &

Hellers, 2000). Furthermore, factors could increase the likelihood of post-operative recurrence of CD include patient smoking, location and behaviour of disease, disease duration before first surgery and prior resections (Gklavas, Dellaportas, & Papaconstantinou, 2017).

Surgical management of perianal disease in CD is frequently needed, in particular anal fissures and fistula-in-ano. Surgical management of anal fissures can be effective, though the potential effect on bowel continence means surgery should be a last resort. Deciding a surgical management plan for anal fistulae can be complex due to the importance of preserving continence and whether or not to divert faeces from the affected area through a temporary ostomy to aid the resolution of perianal disease (Hwang & Varma, 2008). Initial management may involve the use of seton thread, which is passed into the fistula tract to maintain patency and allow drainage which reduces inflammation (Adegbola *et al*., 2018). Further surgical management depends on whether the fistula infiltrates the anal sphincter, as there is a risk of causing faecal incontinence. Surgical management of 'low' fistulae, which are fistulae that do not affect the anal sphincters, involves fistulotomy. The fistula is divided and opened to allow healing. For 'high' fistulae that do affect the anal sphincters, sphincter-saving treatment includes the use of fibrin glue to induce blood clot formation in the fistula track or inserting a fistula plug made of porcine small intestinal mucosa to encourage cell growth within the fistula (Adegbola *et al*., 2018).

Urgent surgical management of UC is largely indicated for severe, intractable colitis which can be identified using the Truelove-Witts criteria as described in section 2.9. Features include fever, numerous bloody stools and signs of haemodynamic instability or the presence of toxic megacolon. Toxic megacolon was discussed in section 2.4. In refractory colitis, a total proctocolectomy with end ileostomy is a common procedure as the diseased bowel is removed and the complications of anastomoses and pelvic dissection are avoided (Hwang & Varma, 2008).

With regards to elective surgery, the risk of malignancy is the most common indication, a cumulative risk which according to a 2001 meta-analysis increases from 2% at 10 years to 18% at

30 years following UC diagnosis (Eaden, Abrams, & Mayberry, 2001). A restorative proctocolectomy with ileal pouch-anal anastomosis is the procedure of choice, as it removes the diseased bowel whilst maintaining a normal defecation pathway, though sometimes a second operation to close the diverting loop ileostomy is needed in the future. Pouchitis is a long-term complication of the ileal-pouch anastomosis and can cause perineal pain and cramping. This can be managed with antibiotics like metronidazole and ciprofloxacin, though a small number of people may need pouch excision. Anti-diarrhoeal medications may be indicated in people with altered bowel function, including increased frequency of defecation and episodes of incontinence (Hwang & Varma, 2008).

2.12 Impact of inflammatory bowel disease

The impact of IBD on an individual's life can be profound. A review of twenty-three studies focussing on living with IBD identified key themes raised by participants as problems they faced as a result of their IBD, including living in fear of complications, experiencing fatigue and living in secrecy due to a lack of public awareness about the condition (Fourie, Jackson, & Aveyard, 2018). The over-arching conclusion from a 2012 meta-analysis was that people with IBD try to 'push' to live a normal life, by controlling the aspects of life that they could, but are 'pulled' back by their IBD due to fears surrounding incontinence, social isolation and difficulties managing fatigue (Kemp, Griffiths, & Lovell, 2012). Such issues are also evidenced in a survey undertaken by Ghosh and Mitchell (2007), participants described their symptoms of IBD as having a large impact on work and leisure activities. Of the 3025 participants in the study with CD, 348 had weekly symptom flare-ups, along with 162 of the 2333 UC participants. Additional examples of the concerns expressed by the participants related to bowel incontinence, sexual relationships and feeling disadvantaged at work (Ghosh & Mitchell, 2007). Similarly, in interviews and focus groups conducted by Hall, Rubin, Dougall, Hungin and Neely, participants described feeling like their bodies were 'under attack' from a disease affecting all aspects of their lives as they had concerns regarding the availability of toilets,

incontinence and feeling unhygienic. Attempts to maintain normality around others was also raised, as participants felt reluctant to discuss their condition for fear of worrying or burdening others and being an embarrassment (Hall, Rubin, Dougall, Hungin, & Neely, 2005).

As discussed in Chapter 1, IBD can have financial implications. McMullan *et al*. interviewed twenty-eight participants with UC and some expressed concerns about their ability to continue working. They recounted needing to change employment, wake earlier to allow additional time to manage symptoms and reduce hours because of fatigue, which then placed a financial burden on themselves and their families (McMullan *et al*., 2017). Furthermore, the management of IBD can also affect patient quality of life, as a study conducted in the USA found that quality of life decreased with the presence of side effects, which were more common in patients taking multiple medications, particularly steroids (Cross, Lapshin, & Finkelstein, 2008). In a study by Kemp *et al*., participant satisfaction with their IBD management appears mixed, with some stating that regular follow-up visits were an unnecessary burden when their condition was in remission. When asked their opinion about self-management for their condition, those with more severe disease were reluctant to make medical decisions without consulting a medical professional first. In addition, participants were asked about integrated IBD care with their specialist and their GP. Many were more comfortable to discuss their condition with a specialist, particularly when their GP admitted they were not as knowledgeable about IBD, though GP-led care with specialist IBD team involvement was considered acceptable (Kemp, Griffiths, Campbell, & Lovell, 2013). Finally, the mental health impact of IBD has also been explored, as anxiety amongst IBD patients appears to be common and is largely linked to the episodic nature of the disease and availability of toilets, which is problematic for participants even in remission. On occasion, some participants described avoiding excessive anxiety by not leaving the house, which contributes to low mood and social isolation. Low mood was also linked to stigma surrounding the condition and lack of knowledge amongst peers (Jordan, Ohlsen, Hayee, & Chalder, 2018). Whilst there is a wealth of qualitative

research investigating the individual impact of IBD on the patient, there is an absence of that examining delays in IBD diagnosis, highlighting the novelty of the research conducted in this thesis.

2.13 Diagnostic delay in inflammatory bowel disease

As outlined in Chapter 1, despite the appreciation that there are delays in the diagnosis of IBD, there is no clear consensus regarding the absolute length of delay. The median diagnostic delays reported in existing literature is varied, ranging from two months to over twelve months for both CD and UC (Basaranoglu et al., 2015; Langholz, Munkholm, Nielsen, Kreiner, & Binder, 1991a; Pellino et al., 2015). In addition, a certain proportion of patients within some studies have reported experiencing prolonged diagnostic delays upwards of two decades (Burisch, 2014; Yang et al., 2000). The changes in diagnostic delay in IBD over time have been reported by some studies although findings are conflicting, so collating the delay values from all existing literature may provide a clearer insight into whether diagnostic delays have changed over time (Cantoro et al., 2017; Romberg-Camps et al., 2009).

Besides a lack of clarity around the extent of this delay, it is unknown what characteristics can influence it. Examples may include variance in presenting symptoms, clinical competence, geographical location and certain participant demographics like age (Burisch, 2014; Harper, McAuliffe, & Beeken, 1986; Novacek *et al.*, 2019). Such characteristics of delay can be considered patient- or healthcare-related based on the level at which the delay occurs, which is explored further in Chapter 3. The impact that delays in diagnosis can have on the clinical course of IBD have been demonstrated in various research, where delays were associated with increased surgery rates and likelihood of complicated disease, as discussed in section 1.3 (Li et al., 2015; Moon et al., 2015).

2.14 Chapter summary

This chapter demonstrates the complexity of IBD, particularly the range of presenting symptoms, presence of EIMs and challenges in diagnosis. In order to make a diagnosis of IBD, clinicians must piece together blood test results, radiological and endoscopic findings to reach the diagnosis. The delays taken to reach this diagnosis may have a detrimental effect on the person's IBD, as medication and other management options are also delayed. Consequently, complications can arise, such as strictures and fistulae in CD, which may require surgery to manage. The extent at which the diagnosis of IBD is delayed should be established and combining this with possible reasons for delay provides a platform from which future research can be conducted to reduce delays and possibly improve clinical outcomes.

The next chapter explores the extent of diagnostic delay through the completion of a systematic review. The methodology followed to conduct the systematic review is outlined, as well as the data analysis of the included articles.

3. Extent of Diagnostic Delay in Inflammatory Bowel Disease- A Systematic Review

A systematic review was conducted to explore the extent of diagnostic delay in Inflammatory Bowel Disease (IBD). The methodical approach taken to perform a systematic review allows for a thorough and reliable analysis of existing literature in a chosen field to answer a specific research question.

3.1 Systematic review overview

Evidence-based medicine involves basing decisions of patient care on the best clinical evidence, which could be evidence into the accuracy of certain investigations, prognostic factors or preventative measures (Sackett, 1997). Consequently, a high volume of research exists and the rapid rate at which literature is published makes it impossible for healthcare professionals to keep abreast of. For example, in Medline alone, over 904636 citations were added in 2018 (US National Library of Medicine, 2019). It would be immensely time-consuming for an individual to locate and read every piece of literature on a given topic. A systematic review provides an excellent solution to this problem as they answer a specific research question by collating the literature and drawing overall conclusions.

The decision was made to conduct a systematic review because it allows the assimilation of all existing data on the diagnostic delay of IBD to be presented within one analysis. The risk of bias is reduced, because of the defined, structured methodology by which a systematic review is completed, for example selecting inclusion and exclusion criteria prior to undertaking the search and quality appraising included articles to highlight to the reader the quality of the described study design (Katikireddi, Egan, & Petticrew, 2015). Additionally, systematic reviews can be reproduced in

the future and the similar results should be found, as the standardised process by which it was completed should be described to the reader (Gopalakrishnan & Ganeshkumar, 2013). The ability for researchers to update systematic reviews is crucial to allow clinical guidelines to develop over time, particularly with advancing medicine.

3.2 Methods

3.2.1 Protocol

Completing a protocol before the systematic review is commenced is important as it outlines the review and clarifies the aims. The protocol provides an overall structure to the review process. Within the protocol, aspects like inclusion and exclusion criteria, databases to search and methods of quality appraisal are confirmed. A comprehensive protocol for this systematic review was produced to ensure transparency and reproducibility (Moher et al., 2015). To reduce the chance of duplicating ongoing or published systematic reviews that answer a similar research question to the one devised for this thesis, PROPSERO was searched for similar protocols as well as a scoping search in PubMed. Once originality of this review was confirmed, it was registered with PROSPERO- an international register for systematic reviews, and can be found at the following: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=108886 (Reference number- CRD42018108886).

The protocol was based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Moher et al., 2015). The protocol was revised with advice from co-author JP and a member of the systematic review team at the Research Institute for Primary Care and Health Sciences (RI) at Keele University (OB). The protocol is included in **Appendix 1**.

3.2.2 Inclusion criteria

Selection of articles was dictated by the presence or absence of defined inclusion and exclusion criteria outlined within the protocol. The reviewers collaborated to devise the inclusion and exclusion criteria, ensuring that everyone understood the criteria to reduce the risk of ambiguity during the review process. The research aims provided the foundation of the criteria, which is outlined using the PICOS framework in **Table 3.2.1** (Methley, Campbell, Chew-Graham, McNally, & Cheraghi-Sohi, 2014). Alongside the inclusion or exclusion based on participant characteristics and study design, selection based upon publication format was also exercised, as certain publications were considered more relevant than others.

3.2.2.1 Primary outcome

The main outcome of this systematic review was to establish the extent of diagnostic delay for IBD, CD and UC. Therefore literature that was included in the systematic review demonstrated a quantified time period of delay from the onset of symptoms to diagnosis. It was anticipated that delay data for IBD would be reported in median and mean values, as these have been used to explore delay in other conditions, including giant cell arteritis (Prior et al., 2017).

3.2.2.2 Secondary outcomes

Further outcomes of this systematic review include exploring consultation and healthcare delays; defined as the time between the patient experiencing symptoms to seeking medical advice and the time between seeking medical advice to receiving a diagnosis. Where possible, comparisons were made between diagnostic delay and IBD phenotype, geographical location and age of patients.

3.2.3 ***Exclusion criteria***

Articles that did not provide a definition of diagnostic delay were excluded, as were those that only included diagnostic delay from when participants first presented to their doctor, for example. Conditions such as indeterminate colitis (IC), ischaemic colitis and Irritable Bowel Syndrome (IBS) were excluded. Although IC is considered IBD, the aim was to include research with a clear IBD diagnosis, therefore if a paper only discussed a diagnostic delay of IC it was excluded. Case studies or series with less than ten participants were excluded from the review as they poorly represent the population of people with IBD. Editorials, conference abstracts, systematic reviews and literature reviews were excluded as the aim was to obtain peer-reviewed primary research.

Table 3.2.1- The inclusion and exclusion criteria, presented using the PICOS framework

	Inclusion Criteria	**Exclusion Criteria**
Population	Confirmed diagnosis of IBD, CD or UC	No diagnosis of IBD Diagnosis of other forms of colitis (ischaemic, eosinophilic, microscopic)
Intervention	N/A	N/A
Comparator	N/A	N/A
Outcome	Defined time period of delay from symptom onset to diagnosis	No time period of delay
Study Design	Cross-sectional study Cohort study Case-control study	Case study/ case-series with <10 participants Animal studies
Publication Type	Full-text, peer-reviewed literature	Conference abstracts Editorial/author comments Systematic review Literature review Articles not in English that cannot be translated

3.2.4 Databases

The following databases were searched- Medline and EMBASE were searched from inception (1974) to 2018 as well as Cumulative Index to Nursing and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The platform used to search Medline and EMBASE was Ovid and CINAHL was accessed using Healthcare Databases Advanced Search.

Medline is an American-based database containing a large volume of literature from health, biomedical and life sciences. EMBASE contains articles with a biomedical or pharmaceutical background. As IBD is considered a condition with multidisciplinary management, using CINAHL was deemed worthwhile as the focus of its articles are on nursing or allied health professionals. Using these databases ensured the completion of a comprehensive systematic review by gathering relevant biomedical literature. The EMBASE search was carried out on the 16th October 2018 and both the CINAHL and Medline searches on 18th October 2018.

3.2.5 Search strategy

The search strategy (**Appendix 2**) was used to identify articles from the databases. Search terms were formulated with assistance from the supervisory team (JP, BS and AF) and the systematic review team at the RI (NC). Search terms for 'diagnostic delay' were based on previous systematic reviews that explored the diagnostic delay of cancer and giant cell arteritis alongside new terms (Neal et al., 2015; Prior et al., 2017).

3.2.6 Creating the search terms

A variety of search terms for IBD and diagnostic delay were devised and Medical Subject Headings (MeSH) were also used. These are used by databases to categorise articles based on topic and they

can be ‘exploded’ to expand the search to include terms associated with the MeSH word. For instance, when the MeSH term ‘inflammatory bowel disease’ is ‘exploded’, ‘Crohn’s Disease’, ‘experimental inflammatory bowel disease’ and ‘ulcerative colitis’ terms are also searched for. The MeSH terms used in the strategy included ‘inflammatory bowel diseases’, ‘colitis’, ‘delayed diagnosis’ and ‘early diagnosis’. ‘Early diagnosis’ was included to identify articles that may make reference to a delayed diagnosis in research of an early diagnosis.

Alongside MeSH terms, free text search terms were used to search article titles, abstracts and keywords, which outline the desired subject of the search. Searching titles, abstracts and keywords was achieved by using the function “.ti,ab,kw” at the end of each search term. The combinations of terms used to search for IBD include ‘inflammatory bowel disease*’, ‘crohn*’, ‘ibd’ and ‘inflam* colitis*’. To do a thorough search for diagnostic delay examples of the terms used are ‘diagnos* adj3 delay*’, (late* OR earl*) adj3 refer*’ and ‘delay* adj3 consult*’, based upon the aforementioned systematic reviews. The adj3 function searched for articles where the selected words appeared within two words of one another.

3.2.7 Combining the search terms

Joining together the search terms for IBD and diagnostic delay was done using Boolean functions (Bramer, de Jonge, Rethlefsen, Mast, & Kleijnen, 2018). All terms for IBD were linked using the ‘OR’ command, to show all articles which reference any term used to describe IBD included in the search strategy. This was repeated for diagnostic delay terms. Then, both of these combined searches were simultaneously searched using the ‘AND’ command which identifies articles associated with both diagnostic delay and IBD. This process was repeated across each database.

3.2.8 Search limits

There was only one limit imposed on the search, where the Boolean 'NOT' function was used to reduce the number of animal studies. This was done by searching for 'exp animals/NOT humans/' and then applying the 'NOT' function to this search.

Search limits were not applied to the other exclusion criteria, for example ischaemic colitis, as any papers that contained exclusion criteria were identified and excluded during the review phase.

3.2.9 Article storage- Mendeley

Mendeley (version 1.16.1, Mendeley Ltd) was the referencing software used to manage the articles sourced from the search strategy. This particular referencing software was chosen because of the ability to manage a high volume of articles and the option to store references on a desktop program. Citations from the database searches were exported to Mendeley using Research Information System file formats. Duplicates were deleted using the inbuilt duplicate program, which occurs when citations are imported. Close duplicates were checked manually to ensure correct deletion of duplicates. When assessing close duplicates, Mendeley provides a percentage confidence when articles are possible duplicates and the interface shows the title, authors and abstract simultaneously to facilitate the manual check.

3.2.10 Article review

Rayyan was used to manage each stage of the review (Ouzzani, Hammady, Fedorowicz and Elmagarmid, 2016). A screenshot of the Rayyan interface is presented in **Figure 3.2.1**. This online interface allows each reviewer to access all uploaded articles and work through each review stage, indicating which articles should be included or excluded and to also provide the reason for this choice. Rayyan also has an inbuilt duplicate program. Other reviewers can be invited to access the

articles, which facilitates the multiple reviewer process. In addition, there is the option to blind the decisions made by other reviewers when the review stage is ongoing and un-blind to allow the resolution of conflict between reviewers. Data from the review can be collected, including the number of articles that were included and excluded and at what point in the review process, for example title or abstract. The data from this feature is included in the PRISMA flowchart **(Figure 3.3.1).**

A simultaneous title and abstract review was conducted by EC and JP, who reviewed 50% each. The article title was read first, with the abstract being reviewed if the title was relevant. If excluded, the article was labelled with a reason for exclusion, for example 'review article' or 'wrong study design' and at which point this happened- 'title' or 'abstract'.

Once the initial review was completed, a second review of the included and excluded abstracts was carried out, with EC and JP reviewing all abstracts. In the event of conflict, the reviewers met to decide whether these articles should be included or excluded.

The full-text review was conducted by four reviewers (EC, JP, BS, AF), with EC reviewing 100% of the articles and JP, BS and AF second-reviewing approximately one third of the articles each. Again, EC and JP resolved any conflicts.

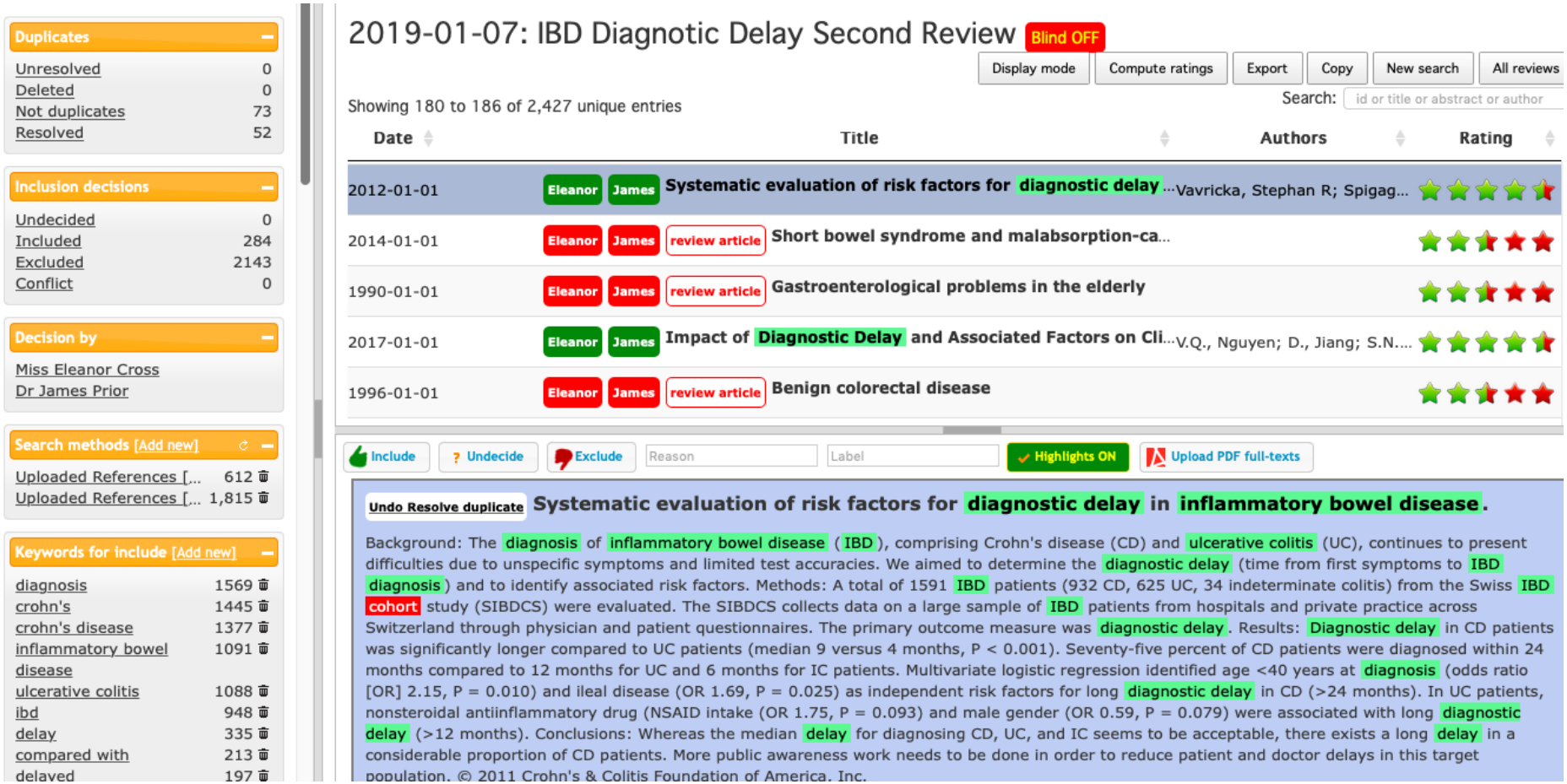


Figure 3.2.1- *A screenshot of the Rayyan QCRI literature management website, retrieved from Rayyan QCRI*

3.2.11 Paediatric papers

In light of the large volume of literature identified by this review and the time constraints in which to complete it, the decision was made to exclude paediatric papers from the systematic review. Although paediatric IBD is an important issue, the scope of the review was restricted to the adult IBD population to ensure the volume of findings were extracted thoroughly and an accurate benchmark for adult IBD could be found. However, with regards to dissemination of research findings, a systematic review of these paediatric articles will form a separate publication.

3.2.12 Foreign language papers

Twenty-seven papers included in the search were non-English language. Staff and students at the RI were emailed to generate help with reviewing and extracting data from these papers. Of these twenty-seven papers, fifteen were adult IBD papers. Languages included Italian, French, German and Spanish. An abbreviated data extraction form was distributed to volunteers so that the reviewers could establish whether the article met the inclusion criteria. Data was extracted from included articles by the same volunteer. Of the fifteen papers, three were included in the review. In addition to assistance from volunteer reviewers, Google translate was used on the three included papers to adequately complete the data extraction and quality appraisal.

3.2.13 Data extraction

In order to ensure the extraction of the important data from the articles, a data extraction form was developed and trialled (**Appendix 3**). Following a discussion with supervisors and alterations to the document, both JP and EC completed the data extraction. JP extracted the data from 4 papers and reviewed 38% of the data extraction completed by EC to identify any errors or omitted data.

Key data included in the extraction form was participant demographics, study design and mean or median values for diagnostic delay.

3.2.14 Converting delay data

To allow comparisons of delay between studies, the decision was made to present all data on delay in months, as the majority of papers displayed median data in this format. The data presented in years tended to be overall ranges of delay, so using a smaller unit of time was beneficial for data interpretation of median and mean values. Conversion was done by multiplying delay data in years by twelve and dividing data in days by thirty. Thirty was chosen as it is the mean length of each month.

3.2.15 Quality appraisal

The quality appraisal of the literature is an essential component to the systematic review process when forming conclusions about the findings. When conducting research, there are many opportunities for bias to be introduced, particularly with the selection process, data processing and reporting of results (Pannucci & Wilkins, 2010). As such, the quality appraisal of literature is an essential component to the systematic review process when forming conclusions about the findings. The Newcastle-Ottawa Scale (NOS), which was developed for appraising cohort and case-control studies, was used (Wells et al., 2014). It has also been adapted for use on cross-sectional studies (Herzog et al., 2013). There are differences in the scoring system between the cohort and cross-sectional NOS, which is discussed further in section 3.3.2. It is a commonly used and reliable method of appraisal (Luchini, Stubbs, Solmi, & Veronese, 2017). The NOS for both cohort and cross-sectional studies is divided into three categories- selection, comparability, and outcome. Within each of these categories, there are statements or questions to be answered by the appraiser. Each

statement is ordered by quality, and the statements deemed high quality by the authors of the NOS are awarded star(s), according to the scale.

Both EC and JP independently appraised the included literature and combined results, which was reviewed by EC to resolve any conflict. The NOS frameworks for cohort and cross-sectional studies were used and have been included in **Appendix 4** and **Appendix 5** respectively.

3.2.15.1 *Quality appraisal of the cohort studies*

The first domain appraises the risk of selection bias, which is when differences in outcome occur within the selected sample and the overall population, commonly due to inappropriate selection and participant attrition (Hernan, Hernandez-Diaz, & Robins, 2004). In the NOS, there are four items that comprise the selection category and the two items used in the appraisal of the articles in this systematic review were the "representativeness of the exposed cohort" and "ascertainment of exposure", which was having a diagnosis of IBD. There were two items that were excluded, which were "selection of the non-exposed cohort" as there was only 1 article including a group of participants that did not have IBD, and "demonstration that the outcome of interest was not present at start of study"; all participants recruited for studies had a prior diagnosis of IBD so information on diagnostic delay was already available. The second domain, comparability, was excluded from the appraisal of these articles, as "comparability of cohorts on the basis of the design or analysis", where the study controlled for age, gender and other factors was not important when assessing diagnostic delay. Additionally, many of these articles were large population cohort studies collecting data from all people with IBD in a specific area and did not recruit controls. Outcome was the final domain used in the quality appraisal process, made up of three items. The only item used in this category was "assessment of outcome", which relates to where the information regarding diagnostic delay was sourced. The other two items were "was follow-up long enough for outcomes to occur?" and "adequacy of follow up of cohorts". As

previously outlined, data on diagnostic delay was provided before study commencement so integrity of follow-up was not important.

3.2.15.2 *Quality appraisal of the cross-sectional studies*

As above, the first category of the NOS for cross-sectional studies aims to identify selection bias. This was done by using three of the four items in the selection category, which were "representativeness of the sample", "sample size" and "ascertainment of exposure (risk factor" were used in the appraisal process. An item assessing comparability of respondents and non-respondents was omitted, as non-respondents were not discussed in any cross-sectional study in this systematic review. The first item assessed whether the sample size was representative of the population, whether the sample size was justified, comparability between respondent and non-respondent characteristics and how the exposure of IBD was identified. The comparability category was omitted from this appraisal, as this was not important when assessing diagnostic delay. The only item used to assess outcome was "assessment of the outcome", as providing diagnostic delay data did not require "statistical testing", which was the other item under outcome.

3.2.16 Data analysis

In order to collate the findings from this systematic review, narrative synthesis was used. This involved producing a descriptive piece of text to outline the key findings from the review, describing to the reader the characteristics within the included articles to strengthen the conclusions drawn.

The guidance of how to complete a narrative synthesis, which had been devised by Popay *et al*. (2006), was followed where appropriate in order to reduce the risk of generating biased or

inaccurate conclusions from the data. This risk arises because of an absence of defined methodological frameworks that should be followed when completing a narrative synthesis (Popay et al., 2006). Using this guidance as a foundation ensured attempts to reduce reporting bias. The guidance adopted in this narrative synthesis was to provide a 'textual description of studies' 'tabulation' of the included studies, to present key information from each study in 'groups and clusters' based on IBD phenotype and the presence of healthcare or consultation delay data, as well as sub-group analyses to look for any connections between the data. The data provided on consultation and healthcare factors for delay was also analysed.

Where possible, the primary outcome, which is the reported time-period of diagnostic delay, will be pooled using meta-analysis methods, which is an analytical method to reach conclusions about the pooled data set (Haidich, 2010). If applicable, sensitivity analysis will also be performed.

3.3 Results

Following the database search, 7362, 2781 and 447 articles were sourced from EMBASE, Medline and CINAHL respectively. Of these 10,590 articles, 3020 duplicate articles were deleted. This left 7570 to undergo title and abstract review, with 5127 studies being excluded based on title. The abstracts of 2443 articles were reviewed and 2143 of these were excluded. The remaining 300 studies were included in a full text review. Following the exclusion of ninety-three conference abstracts, seven articles where full texts were not sourced and four papers which were not translated, the remaining 196 full texts were sourced and reviewed. Thirty-five papers met the inclusion criteria and this data was extracted.

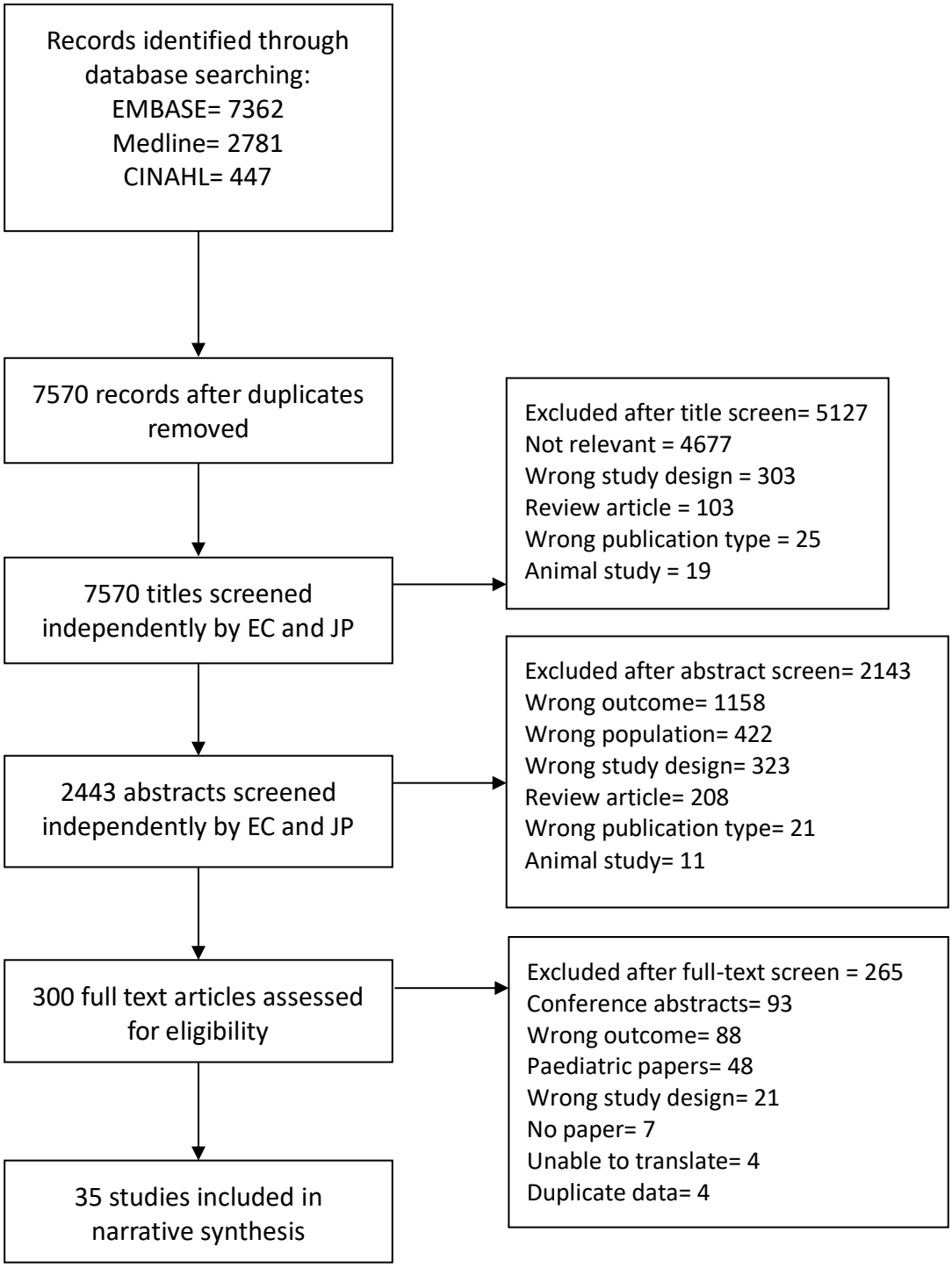


Figure 3.3.1- *A flow chart demonstrating the screening process of the studies identified from the search strategy, based on the inclusion and exclusion criteria. Adapted from 'Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement'*

3.3.1 ***Characteristics of included studies***

Thirty-five articles were included in the systematic review (**Table 3.3.1**). Twenty-nine were cohort studies (83%), of which nine were prospective (31%), eighteen were retrospective (62%) and two studies (7%) combined both approaches. The remaining six papers (17%) were cross-sectional. Publication dates ranged from 1971 to 2019, with eighteen being published from 2010 onwards.

In total, the number of participants included in the articles comprised within this systematic review was 14,524. There was one article that provided information regarding the diagnostic delay of IBD but not related specifically to delays in CD or UC (Parente et al., 2015) . The total number of participants from this study was 252. The remaining studies did provide information of the diagnostic delays of either or both CD and UC. The overall number of CD participants within these studies was 9170 and for UC, this number was 7311.

The studies represent wide variation in geographical area, including seventeen (49%) from European and eleven (31%) Asian countries. Five articles (14%) were from North America including the USA and Canada; and one (3%) from South America. One article (3%) was from Africa. Two articles (6%) originated from the United Kingdom, four (12%) from Italy, three (9%) from the USA and two (6%) from Iran.

The studies were conducted in a range of healthcare settings. The majority of studies were carried out in either a secondary (n= 22, 63%) or tertiary care (n= 7, 20%) setting, whilst six (17%) utilised population registries.

Finally, the criteria used to diagnose IBD was provided by most included studies. This largely centred around the fulfilment of certain presenting symptoms, radiologic and histologic findings (n= 14, 40%). Studies also used the Lennard-Jones criteria (n= 4, 11%) for CD and the Copenhagen Diagnostic Criteria for CD (n= 2, 6%) and UC (n=2. 6%).

Table 3.3.1*- An outline of the characteristics of the included studies in this systematic review*

Author and Publication Year	Country	Study Design	Recruitment Period	Healthcare Setting	Diagnostic Criteria for IBD
Kyle (1971)	Scotland	Cross-sectional	1955-1969	Not reported	CD= history and examination findings, brief use of radiology/endoscopy
Lind 1985)	Norway	Prospective cohort	1975-1979	Secondary	CD= standardised investigational program (colonoscopy/gastroscopy. Biopsy, barium enema)
Foxworthy (1985)	USA	Prospective cohort	1975-1983	Secondary	CD= clinical presentation/course, radiologic/histologic/laparotomy appearance
Harper (1986)	USA	Cross-sectional	1983-1984	Secondary	CD= typical symptoms/findings, radiologic/endoscopic/operative features
Di Simone (1987)	France	Retrospective cohort	Not reported	Not reported	UC= not reported
Lee (1987)	England	Retrospective cohort	1969-1983	Secondary	CD= clinical records, histopathological diagnostic index from consultant colleagues
Sategna-Guidetti (1990)	Italy	Retrospective cohort	1965-1988	Secondary	CD= classical criteria
Langholz (1991)	Denmark	Prospective cohort	1962-1987	Secondary	UC= Copenhagen criteria
Munkholm (1992)	Denmark	Prospective cohort	1962-1987	Secondary	CD= Copenhagen criteria
Wright (1992)	South Africa	Prospective cohort	1970-1988	Secondary	CD= compatible clinical, radiologic, endoscopic, histologic features
Wengrower (1997)	Israel	Prospective cohort	Not reported	Military recruits	CD= clinical, laboratory, radiographic, endoscopic, histological features
Yang (2000)	Korea	Retrospective + prospective cohort	1986-1977	Secondary	UC= diarrhoea, blood/pus in stool, sigmoidoscopy, histological/cytological, radiologic/endoscopic features
Saro Gismera (2003)	Spain	Retrospective + prospective cohort	1954-1977	Secondary	CD= Lennard-Jones criteria UC= Truelove criteria (severity)

Aghazadeh (2004)	Iran	Retrospective cohort	1992-2002	Secondary	CD= Lennard-Jones UC= not reported
Burgmann, (2006)	Canada	Cross-sectional	2004-2005	Manitoba IBD registry	CD= ICD codes UC= ICD codes
Albert (2008)	Germany	Cross-sectional	2005-2007	Patient organisation	CD= not reported
Romberg-Camps (2009)	Netherlands	Prospective cohort	1991-2002	Population registry	CD= Lennard-Jones criteria UC= continuous mucosal inflammation without granuloma, affecting rectum +/ some/ all of the colon in continuity with rectum
Roth (2010)	Canada	Retrospective cohort	1996-2001	Secondary	UC= not reported
Jain (2012)	India	Retrospective cohort	2005-2010	Secondary	CD= not reported UC= not reported
Vavricka (2012)	Switzerland	Retrospective cohort	2006-2009	Population registry	CD= not reported UC= not reported
Taghavi (2013)	Iran	Prospective cohort	1989-2009	Population registry	CD= Lennard-Jones UC= not reported
Burisch, 2014	Europe	Prospective cohort	Jan 2010-Dec 2010	Secondary	CD= Copenhagen diagnostic criteria UC= Copenhagen diagnostic criteria
Pellino, 2015	Italy	Cross-sectional	2000-2009	Secondary	CD= accepted ECCO criteria
Li (2015)	China	Retrospective cohort	2010-2014	Secondary	CD= colonoscopy, enteroscopy, capsule endoscopy, histopathology, haematology
Parente (2015)	Brazil	Retrospective cohort	2011-2012	Secondary	IBD= World Gastroenterology Organisation guidelines
Moon (2015)	Korea	Retrospective cohort	2000-2008	Cohort study register	CD= clinical, endoscopic, radiologic, histologic findings
Maconi (2015)	Italy	Retrospective cohort	2012-2013	Primary and secondary	CD= not reported
Basaranoglu (2015)	Turkey	Retrospective cohort	1995-2007	Tertiary	CD= clinical, radioscopic, endoscopic, histologic findings UC= not reported
Lin (2015)	Taiwan	Retrospective cohort	1991-2014	Not reported	UC= not reported

Lee (2017)	South Korea	Retrospective cohort	2000-2015	Secondary	CD= not reported (Montreal classification for disease severity at diagnosis) UC= not reported (Montreal classification for disease severity at diagnosis)
Cantoro, 2017	Italy	Retrospective cohort	1955-2014	Secondary	CD= not reported (Montreal classification for disease severity at diagnosis) UC= not reported (Montreal classification for disease severity at diagnosis)
Nguyen (2017)	USA	Retrospective cohort	2008-2015	Tertiary	CD= not reported (Montreal classification for disease severity at diagnosis) UC= not reported (Montreal classification for disease severity at diagnosis)
Szanto (2018)	Hungary	Retrospective cohort	2007-2015	Tertiary	CD= Lennard-Jones and accepted ECCO criteria UC= Lennard-Jones and accepted ECCO criteria
Banerjee (2018)	India	Retrospective cohort	Not reported	Secondary	CD= not reported (Montreal classification for disease severity at diagnosis) *paediatric CD= Porto criteria
Novacek, 2019	Austria	Cross-sectional	2014-2015	Secondary	CD= ECCO criteria UC= ECCO criteria

Key: IBD; Inflammatory Bowel Disease, CD; Crohn's Disease, UC; Ulcerative Colitis, ECCO; European Crohn's and Colitis Organisation

3.3.2 ***Quality appraisal***

3.3.2.1 Appraisal of the cohort studies

The twenty-nine cohort studies were appraised (**Table 3.3.2**). Most studies were either "somewhat representative" or "truly representative", a decision made depending on the geographical spread of recruitment. For example, Vavricka *et al.* (2012) sampled from an IBD registry covering all regions of Switzerland so was considered 'truly representative'. However, where studies sampled from only one medical establishment or from one area within a country or town, as with Nguyen *et al.* (2017), they were considered "somewhat representative". Wengrower (1997) was not awarded any stars for this section, as they sampled from a 'selected group of users', which were military recruits. The "ascertainment of exposure" of IBD was determined by assessing "secure records" in twenty-two papers which scored one star, as medical records can be considered reliable. Only one paper provided no description of this. The third domain focusses on the study outcomes. Sixteen studies mainly used either "record linkage" to determine delay and were awarded 1 star, whilst participants in eight studies "self-reported" their diagnostic delay and were awarded no stars as there is a higher risk of recall bias with this method. Five articles provided "no description" of how outcome was assessed and also scored no stars.

Table 3.3.2- *The quality appraisal of the cohort studies, using the abbreviated NOS. The number of stars awarded for each item is included in brackets*

	Selection			Outcome		
Author and Publication Year	**Representativeness of the cohort /1**	**Ascertainment of Exposure /1**	**Number of stars /2**	**Assessment of Outcome**	**Number of stars /1**	**Total number of stars**
Lind, 1985	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Foxworthy, 1985	Selected group of users (elderly population) (0)	Secure records (1)	1	Self-report (0)	0	1
Simone, 1987	No description (0)	No description (0)	0	No description (0)	0	0
Lee, 1987	Somewhat representative (1)	Secure records (1)	2	No description (0)	0	2
Sategna-Guidetti, 1990	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Langholz, 1991	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Munkholm, 1992	Somewhat representative (1)	Secure records (1)	2	No description (0)	0	2
Wright, 1992	Somewhat representative (1)	Secure records (1)	2	No description (0)	0	2
Wengrower, 1997	Selected group of users (military recruits) (0)	Secure records (1)	1	Self-report (0)	0	1

Yang, 2000	Truly representative (1)	Secure records (1)	2	Self-report (0)	0	2
Saro Gismera, 2003	Somewhat representative (1)	Secure records (1)	2	Self-report (0)	0	2
Aghazadeh, 2004	Somewhat representative (1)	Secure records (1)	2	No description (0)	0	2
Romberg-Camps, 2009	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Roth, 2010	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Jain, 2012	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Vavricka, 2012	Truly representative (1)	Secure records (1)	2	Self-report (0)	0	2
Taghavi, 2013	Somewhat representative (1)	Secure records (1)	2	Self-report (0)	0	2
Burisch, 2014	Truly representative (1)	Secure records (1)	2	Self-report (0)	0	2
Li, 2015	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Parente, 2015	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3

Mo Moon, 2015	Truly representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Manconi, 2015	Somewhat representative (1)	Secure records (1)	2	Self-report (0)	0	2
Basaranoglu, 2015	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Lin, 2016	Truly representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Lee, 2017	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Cantoro, 2017	Truly representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Nguyen, 2017	Somewhat representative (1)	Secure records(1)	2	Record linkage (1)	1	3
Szanto, 2018	Truly representative (1)	Secure records (1)	2	Record linkage (1)	1	3
Banerjee, 2018	Somewhat representative (1)	Secure records (1)	2	Record linkage (1)	1	3

3.3.2.2 Appraisal of the cross-sectional studies

The representativeness of the sampled population was determined by the geographical scope of included participants. This was varied across the six articles, as participants from four articles were deemed truly or somewhat representative of the population, though one paper sampled from selected groups of users based on age and one provided no description of the sampling strategy. Scoring whether sample sizes were justified or satisfactory was based on sample sizes and geographical range of participants and whether the paper had discussed the merits or limitations of their sample size. Only the two papers that scored "truly representative" were considered to have justified or satisfactory sample sizes. "Ascertainment of exposure" was scored on the presence or absence of a method used to recruit individuals with IBD. For example, in the study carried out by Burgmann *et al*., participants with IBD were identified by International Classification of Diseases (ICD) codes in their medical records, which is a "validated measurement tool". As Harper *et al*. recruited by viewing the records of gastroenterologists which is highly likely to be reliable, specific information on how these individuals were determined to have IBD was not provided, so this was awarded "tool is available and described" as it was not considered that "no description" had been provided but a there was no discussion of a validated measurement tool. One article provided "no description" of identifying participants with IBD.

For measuring the outcome of diagnostic delay, stars were awarded based on how robust the chosen methods were. Two stars were awarded for "record linkage" or "independent blind assessment", as demonstrated by Pellino *et al.* (2015). "Self-report" scored one star, demonstrating that it is a less robust means of assessing outcomes due to the risk of recall bias. In contrast, the NOS for cohort studies did not award any stars for studies that used "self-report", demonstrating variation between the two scores. This is discussed in section 3.4.1. **Table 3.3.3** contains the appraisal of the cross-sectional studies.

Table 3.3.3- *The quality appraisal of the cross-sectional studies, using the abbreviated NOS. The number of stars awarded for each item is included in brackets*

	Selection				Outcome		
Author and Publication Year	**Representativeness of the cohort /1**	**Sample Size /1**	**Ascertainment of Exposure /2**	**Number of stars /4**	**Assessment of Outcome /2**	**Number of stars /2**	**Total number of stars**
Kyle, 1971	No description of sampling strategy (0)	Not justified (0)	No description (0)	0	No description (0)	0	0
Harper, 1986	Selected group of users (elderly population) (0)	Not justified (0)	Tool is available and described (1)	1	No description (0)	0	1
Burgmann, 2006	Truly representative (1)	Justified/satisfactory (1)	Validated measurement tool (2)	4	Self-report (1)	1	5
Albert, 2007	Somewhat representative (1)	Not justified (0)	Tool is available and described (1)	2	Self-report (1)	1	3
Pellino, 2015	Somewhat representative (1)	Not justified (0)	Validated measurement tool (2)	3	Record linkage (2)	2	5
Novacek, 2019	Truly representative (1)	Justified/satisfactory (1)	Validated measurement tool (2)	4	Self-report (1)	1	5

3.3.3 Diagnostic delay

Data from studies providing diagnostic delays for IBD can be found in **Table 3.3.4** and **Table 3.3.5**. The values extracted from papers providing diagnostic delay data for CD and UC have been presented in three tables, two displaying participant demographics (**Table 3.3.6** for CD, **Table 3.3.7** for UC) and another the values for delay (**Table 3.3.8**). As the data within this systematic review was skewed, the decision was made to focus analysis on median values and interquartile ranges (IQR), following the format of previous literature on delay where asymmetrical distribution of data was also found (Osei, Akweongo, & Binka, 2015). Skewness in data arises when there is variation in the median and mean values. Positive skew arises when the median is smaller than the mean, with negative skew being the opposite. In the context of diagnostic delay, data is often positively skewed as the majority of patients tend to have similar delays with a small proportion experiencing prolonged delay causing their delay to disproportionally contribute to the cumulative delay of all patients (Verhagen, Kapinga, & van Rosmalen-Nooijens, 2010). For transparency, mean values have been included alongside median values within tables but are not discussed further.

3.3.3.1 Diagnostic delay of inflammatory bowel disease

Eight papers provided data on delays in IBD diagnosis. As previously stated, one article provided information reporting the diagnostic delay of IBD only and seven provided further information on delays of CD and UC. These studies used IBD as an umbrella diagnosis, as participants were defined as having CD or UC, the two distinct disease patterns of IBD, but also IC and proctitis. Although participants were defined as having these sub-conditions that comprise IBD, the diagnostic delay provided is of IBD as a whole. With regards to geographical location, five articles (63%) are from European countries, and one each from North America, South America and Asia (13%). Article studies were conducted in a range of healthcare settings, as four were based in secondary care

(50%), two in tertiary care (25%) and two used population data-sets (25%). Most articles reported cohort study designs (75%). All articles provided information on the number of participants with each IBD classification included in the delay, with all papers including participants with both CD and UC. Two of these papers also included IC (25%) with one including IC and proctitis (13%). IBD was diagnosed using a variety of radioscopic or endoscopic findings and criteria, including Lennard-Jones criteria for CD (n= 4, 50%) and ECCO criteria (n=2, 25%). This information can be found in **Table 3.3.1.** Diagnostic delay is comparable across all eight studies, as it is defined as the time interval between symptom onset and diagnosis.

Median values for diagnostic delay of IBD were provided by six articles and ranged from 2 to 96 months. Ninety-six months is considered an outlier as the result is larger than the other values. For instance, the median values from five articles were between 2 and 5.3 (IQR 2.3-16.4) months. A sensitivity analysis has been performed whereby outliers have been excluded, and this is presented in section 3.3.3.6.

Table 3.3.4- *Participant characteristics from the included studies that provide data for the diagnostic delay of IBD, in order of publication year*

					Age	
Author and Publication Year	**Country**	**N**	**Gender % Male**	**When reported**	**Mean age (standard deviation) , y**	**Range, y**
Saro Gismera, 2003	Spain	1018 CD- 415 UC- 565 IC- 38	52.8%	At onset At diagnosis	37.66 (0.97) 39.49 (1.08)	
Burgmann, 2006	Canada	112 CD- 65 UC- 42 Proctitis- 3 IC-2	42.9%	At diagnosis	38 (12.9)	16 - 77
Romberg-Camps, 2009	Netherlands	1187 CD- 476 UC- 630 IC- 81	48.9%	Not reported	CD- 34 UC- 42 IC- 42	CD- 5 – 79 UC- 8 – 84 IC- 13 - 77
Basaranoglu, 2015	Turkey	282 CD- 98 UC- 184	64.2%	At diagnosis	40.1 (14.7)	
Parente, 2015	Brazil	252 CD- 100 UC- 152	43.3%	At onset	35.2 (14.5)	
Cantoro, 2017	Italy	3392 CD- 1537 UC- 1855	53.1%		Not reported	
Szanto, 2018	Hungary	911 CD- 428 UC- 483	46.3%		See CD and UC table	
Novacek, 2019	Austria	1265 CD- 830 UC- 435	49.4%	At time of study	40 (31 – 52) [median (IQR)]	18 - 87

Table 3.3.5- *Converted data for the diagnostic delay of IBD from the included studies, from smallest median delay to largest*

Author and Publication Year	Definition of Diagnostic Delay	Median (IQR)	Mean (SD)	Range
Basaranoglu, 2015	Symptom onset to diagnosis	2	3.1 (2.7)	0 - 18
Cantoro, 2017	First likely symptoms to diagnosis	3 (0 – 13)		
Romberg-Camps. 2009	Duration of symptoms before diagnosis	3		0 - 480
Szanto, 2018	Onset of symptoms to diagnosis	3.6 (0 – 9.6)		
Novacek, 2019	Onset of first IBD-related symptoms to diagnosis	5.3 (2.3 – 16.4)		
Burgmann, 2006	Duration of symptoms before diagnosis	96	135.6	
Saro Gismera, 2003	Symptomatic period before diagnosis		21.96 (3.48)	
Parente, 2015	Onset of clinical manifestations to diagnosis		35.5	

3.3.3.2 Diagnostic Delay of Crohn's Disease

Twenty-five articles from this systematic review provide values of diagnostic delay in CD. The articles arise from four continents- Europe (n= 12, 48%), Asia (n= 9, 36%), North America (n= 2, 8%) and Africa (n= 1, 4%). Twenty articles (80%) were cohort studies and the remaining five were cross-sectional (22%). The research providing CD delay values was conducted in secondary care (n= 13, 52%) secondary and primary care (n=1, 4%) and tertiary care (n= 3, 13%), with seven utilising population data-sets (30%). One article did not provide information on the study setting (Kyle, 1971). Identifying individuals with CD was based upon clinical, radioscopic and endoscopic findings in six articles (27%), Lennard-Jones criteria in five (20%) and ECCO criteria in three (13%). There was no mention of how individuals with IBD were diagnosed in eight papers (35%). Diagnostic delay was comparable across the articles and involved the time between symptom onset to diagnosis. Specific definitions of diagnostic delay for each article can be found in **Table 3.3.8**.

As extracted from seventeen articles, the median delay of CD ranged from 2 to 84 months which contains an outlier of 84 months, as this value is substantially larger than the values for delay extracted from other article. A sensitivity analysis has been performed and which has excluded outliers from the analysis, in section 3.3.3.6. Overall, the range of delay in CD diagnosis was from 1 day to 34 years.

Table 3.3.6*- Participant characteristics from the included studies that provide data for the diagnostic delay of CD, in order of publication year*

					Age	
Author and Publication Year	**Country**	**N**	**% Male**	**When reported**	**Mean (SD), y**	**Range, y**
Kyle, 1971	Scotland	175	38.3%	Not reported		
Lind, 1985	Norway	214	56.1%	At onset	24 [22 median]	7 - 63
Lee, 1987	England	215	34.0%	Not reported		
Munkholm, 1992	Denmark	373	42.1%	At onset	32.5	8 - 84
Wright, 1992	South Africa	239	32.2%	Not reported	31.4 (12.8)	
Wengrower, 1997	Israel	53	62.3%	At diagnosis	19.4	18 - 21
Saro Gismera, 2003	Spain	415	46.5%	At onset At diagnosis	30.68 (1.4) 33.53 (1.51)	
Aghazadeh, 2004	Iran	47	26.6%	At diagnosis	31.9	14 - 83
Burgmann, 2006	Canada	65	33.8%	See IBD table		
Albert, 2007	Germany	112	34.8%	At diagnosis	28 (8.0) Female 31 (11.5) Male	
Romberg-Camps, 2009	Netherlands	476	39.3%	Not reported	34	5 – 79

Jain, 2012	**India**	**12**	**50.0%**	**At diagnosis**	**40**	**21 – 80**
Vavricka, 2012	Switzerland	932	46.8%	Not reported	41 (15)	16 – 88
Taghavi, 2013	Iran	120	49.2%	At diagnosis	32.97 (1.34)	9 – 80
Basaranoglu, 2015	Turkey	98	52.0%	Not reported	37.8 (13.5)	17 – 79
Maconi, 2015	Italy	83	41%	At diagnosis	37.2 (15.3)	14 - 74
Li, 2015	China	343	70.0%	At diagnosis	31.8 (12.5)	
Mo Moon, 2015	Korea	1047	72.3%	At onset	27.7 (12.3)	
Pellino, 2015	Italy	361	Not reported	At diagnosis	32.54 (14.47)	
Lee, 2017	South Korea	165	76.4%	At diagnosis	28.2 (13.8)	
Cantoro, 2017	Italy	1537	Not reported	Not reported		
Nguyen, 2017	USA	110	41.0%	At onset At diagnosis	35 (17) 38 (17)	
Banerjee, 2018	India	720	60.3%	Not reported	[32 (18 – 50) median (IQR)]	
Szanto, 2018	Hungary	428	45.3%	At onset At diagnosis	26.6 (11.3) 30.9 (12.5)	
Novacek, 2019	Austria	830	48.1%	At enrolment	[40 (31 – 52) median (IQR)]	

3.3.3.3 Diagnostic Delay of Ulcerative Colitis

There were seventeen articles that provided information for the diagnostic delay of UC. Eight articles were from European countries (47%), six were from Asian countries (35%) and three from North American countries (18%). They were published between 1987 and 2019. There were fifteen cohort studies studies (88%) and two cross-sectional studies (11%). Nine studies were based in secondary care (53%), three in tertiary care (18%) and population data sets were used in four studies (24%). The study in 1987 did not provide information on the study setting (6%). The diagnosis of UC was not defined in seven studies (54%), whilst ECCO criteria and various clinical, radioscopic and endoscopic findings were used in two (15%). ICD codes and the Copenhagen criteria were present in one study (8%). Diagnostic delay was classified as the time between symptom onset and diagnosis, making the findings comparable.

Regarding delays in UC diagnosis, eleven articles reported median values which ranged from 2 to 114 months, including an outlier of 114 months as it is remarkably different from the other results. A sensitivity analysis has been performed and findings have been presented in section 3.3.6. The overall range of UC diagnostic delay was 3.1 to 135.6 months.

Table 3.3.7- *Participant characteristics from the included studies that provide data for the diagnostic delay of UC, in order of publication year*

					Age	
Author and Publication Year	**Country**	**N**	**% Male**	**When reported**	**Mean (SD), y**	**Range, y**
Simone, 1987	France	111	57.7%	Not reported	34	5 - 73
Langholz, 1991	Denmark	1161	46.7%	At diagnosis	34	2 - 88
Yang, 2000	Korea	94	47.9%	Not reported	[35 median]	8 - 68
Saro Gismera, 2003	Spain	565	48.1%	At onset At diagnosis	42.84 (1.34) 43.95 (1.47)	
Aghazadeh, 2004	Iran	47	56.5%	At diagnosis	30.5	10 - 60
Burgmann, 2006	Canada	42	Not reported	See IBD table		
Romberg- Camps, 2009	Netherlands	630	55.6%	Not reported	42	8 - 84
Roth, 2010	Canada	102	51.0%	At diagnosis	39 (17.9)	9 - 85

Vavricka, 2012	**Switzerland**	**625**	**53.8%**	**At enrolment** **At onset**	**42 (14)** **33 (13)**	**16 – 82** **5 - 82**
Jain, 2012	India	160	78%	Not reported	40.9	
Taghavi, 2013	Iran	620	83.8%	At diagnosis	34.68 (1.44)	
Basaranoglu, 2015	Turkey	184	70.7%	Not reported	41.4 (15.2) [41 median]	14 - 78
Nguyen, 2017	USA	67	44.8%	At onset At diagnosis	44 (19) 45 (19)	
Cantoro, 2017	Italy	1855	Not reported	Not reported		
Lee, 2017	South Korea	130	54.6%	At diagnosis	38.8 (15.6)	
Szanto, 2018	Hungary	483	47.2%	At onset At diagnosis	30.3 (12.4) 30.9 (12.5)	
Novacek, 2019	Austria	435	51.2%	At enrolment	[40 (31 – 51) median (IQR)]	

Table 3.3.8- *Converted data for the diagnostic delay of CD and/or UC from the included studies, from smallest median delay to largest*

		Converted Diagnostic Delay CD (months)			**Converted Diagnostic Delay UC (months)**		
Author and Publication Year	Definition of Diagnostic Delay	Median (IQR)	Mean (SD)	Range	Median (IQR)	Mean (SD)	Range
CD Only							
Wengrower, 1997	Duration of signs/symptoms before diagnosis		4	1 - 36			
Lee, 1987	Interval between onset and diagnosis		11				
Mo Moon, 2015	Interval from first symptoms to established diagnosis		16 (33.1)	0 – 412.4			
Kyle, 1971	Onset to diagnosis interval	6	19	0.03 - 360			
Wright, 1992	Onset of symptoms to diagnosis		21.2 (36.7)				
Maconi 2015	Onset of symptoms to dianosis	8 (3 - 27)		0 - 324			

Li, 2015	Onset of symptoms to diagnosis	10 (2 – 34)	29 (44.3)			
Pellino, 2015	Symptom-diagnosis interval	11		1 - 163		
Albert, 2007	First complaints to establishment of diagnosis	13	29.4 (44)	0 – 281		
Banerjee, 2018	Symptom onset to confirmation of diagnosis	18 (6 – 36)	25.78			
Lind, 1985	Start of symptoms to diagnosis	24	49.2	0 – 372		
Munkholm, 1992	Occurrence of first symptoms to diagnosis	26.4		0 – 324		
UC Only						
Yang, 2000	From onset of symptoms to diagnosis				6	1 - 120

Langholz, 1991	Onset of symptoms to diagnosis				12		0 - 444
Roth, 2010	Time of symptom onset to time of diagnosis					21.6 (54)	0 - 408
Simone, 1987	Appearance of initial symptoms and timing of diagnosis					30	
CD and UC							
Basaranoglu, 2015	Symptom onset to diagnosis	2	3 (2.8)	0 - 18	2	3.2 (2.6)	0 – 15
Lee, 2017	Duration of first symptoms to diagnosis	6.2 (1.5 – 21.5)			2.4 (1.2 – 6.2)		
Romberg-Camps, 2009	Duration of symptoms before diagnosis	5		0 - 360	3		0 - 480
Novacek, 2019	Onset of first IBD-related symptom to diagnosis	6.4 (2.3 – 23.4)			3.4 (1.4 – 10.3)		
Cantoro, 2017	First likely symptoms to diagnosis	7.1			2.0		
Nguyen, 2017	Symptom onset to diagnosis	9.5 (3.8 – 25.6)			3.1 (1.1 – 9.6)		
Vavricka, 2012	From first IBD symptoms to diagnosis	9 (3 – 24)			4 (1 – 12)		

Szanto, 2018	Onset of symptoms to diagnosis	25.2 (0 – 103.2)			55.2 (0 – 123.6)		
Burgmann, 2006	Duration of symptoms before diagnosis	84	121.2		114	150	
Jain, 2012	Onset of symptoms to diagnosis		15.3	1 - 72		1.5	0.2 – 4.8
Saro Gismera, 2003	Symptomatic period before diagnosis		34.2 (6.48)			13.32 (2.76)	
Aghazadeh, 2004	Onset of complaints to definitive diagnosis		17.7			13.9	
Taghavi, 2013	Interval between onset of symptoms and diagnosis		16.56 (14.3)			14.36 (13.1)	

3.3.3.4 Comparing the diagnostic delay of Crohn's disease and ulcerative colitis

There were thirteen papers that compared diagnostic delays of CD and UC. Generally, diagnostic delays of CD were longer than UC. For instance, in a cohort study conducted by Vavricka *et al*. demonstrated a median delay for CD of 9 months (IQR 3 -24) compared to a median delay of 4 months (IQR 1-12) for UC. Similarly, Nuygen *et al*. found that the median delay within their sample was 9.5 months (IQR 3.8-25.6) for CD and 3.1 months (IQR 1.1-9.6) for UC. However, this pattern was not represented in studies by Szanto *et al*., where the median diagnostic delay of CD was 25.2 (IQR 0-103.2) months and 55.2 (IQR 0-123.6) months for UC, or Burgmann *et al*., where median delay was 84 and 114 months for CD and UC respectively.

3.3.3.5 Diagnostic delay over time

The extent of diagnostic delays reported by patients with CD does not appear to have changed over time when ordering articles in ascending year of publication. The oldest paper providing delay data for a CD population was published by Kyle in 1971. They reported a median diagnostic delay of 6 months (Kyle, 1971). However, the range of median values reported in papers published between 2017 and 2019 was 6.4 (IQR 2.3-23.4) to 25.2 (IQR 0-102.3) months. **Figure 3.3.2** demonstrates the diagnostic delay of CD over time. Changes in diagnostic delay of UC are presented in **Figure 3.3.3**.These graphs have been reproduced following exclusion of outliers (section 3.3.3.6). Alternatively, the delay that patients with UC experience appears to be decreasing over time when excluding the 55.2 and 114 month outliers. The oldest paper reporting a median value for delayed diagnosis in UC, published in 1991, was 12 months, which reduced to 6 months in 2000 then to 3.1 (IQR 1.1-9.6) and 3.4 (IQR 1.4-10.3) in 2017 and 2019 respectively.

In a Turin case series of 153 patients with CD conducted by Sategna-Guidetti *et al*., data was provided for diagnostic delay depending on year of diagnosis. This data does demonstrate some improvement in median diagnostic delay. For instance, median diagnostic delay in 1965 to 1977 was 30 months, with an overall range of delay of 0 to 324 months. Between the years 1978 to 1988, the median diagnostic delay had reduced to 24 months, though the overall range was between 0 and 432 months (Sategna-Guidetti & Marucco, 1990). A study by Cantoro *et al*. compared diagnostic delay of IBD between a historical cohort, between 1955 and 1987, and the modern cohort, 1985 to 2014. Although there was no change in diagnostic delay between both the historical and modern cohort, where median delay was 4.0 months (IQR 0 – 24) and 3.0 months (IQR 0.8 – 12) respectively, there was a decrease in the proportion of patients experiencing delays over 24 months in the modern cohort compared to historical.

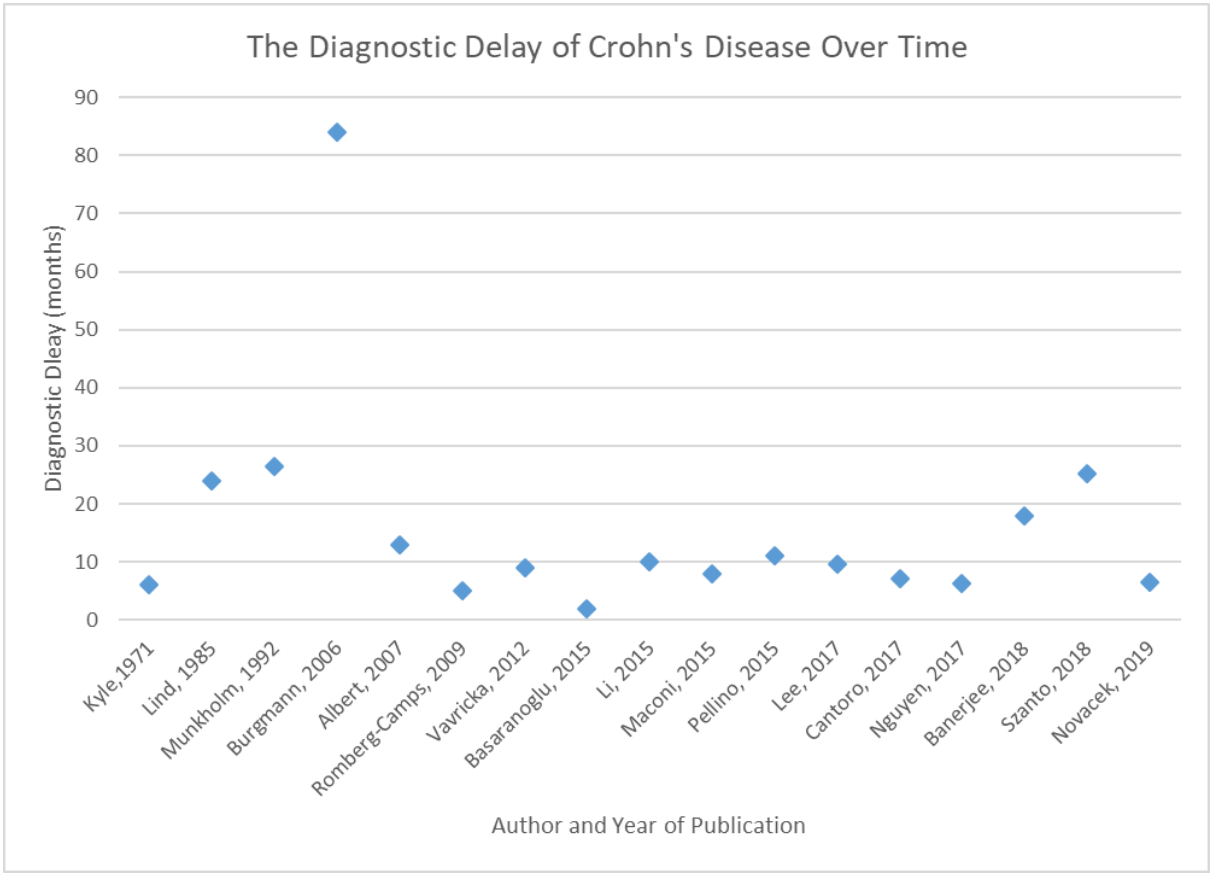


Figure 3.3.2- *A graph showing changes in the extent of diagnostic delay in CD compared to year of publication*

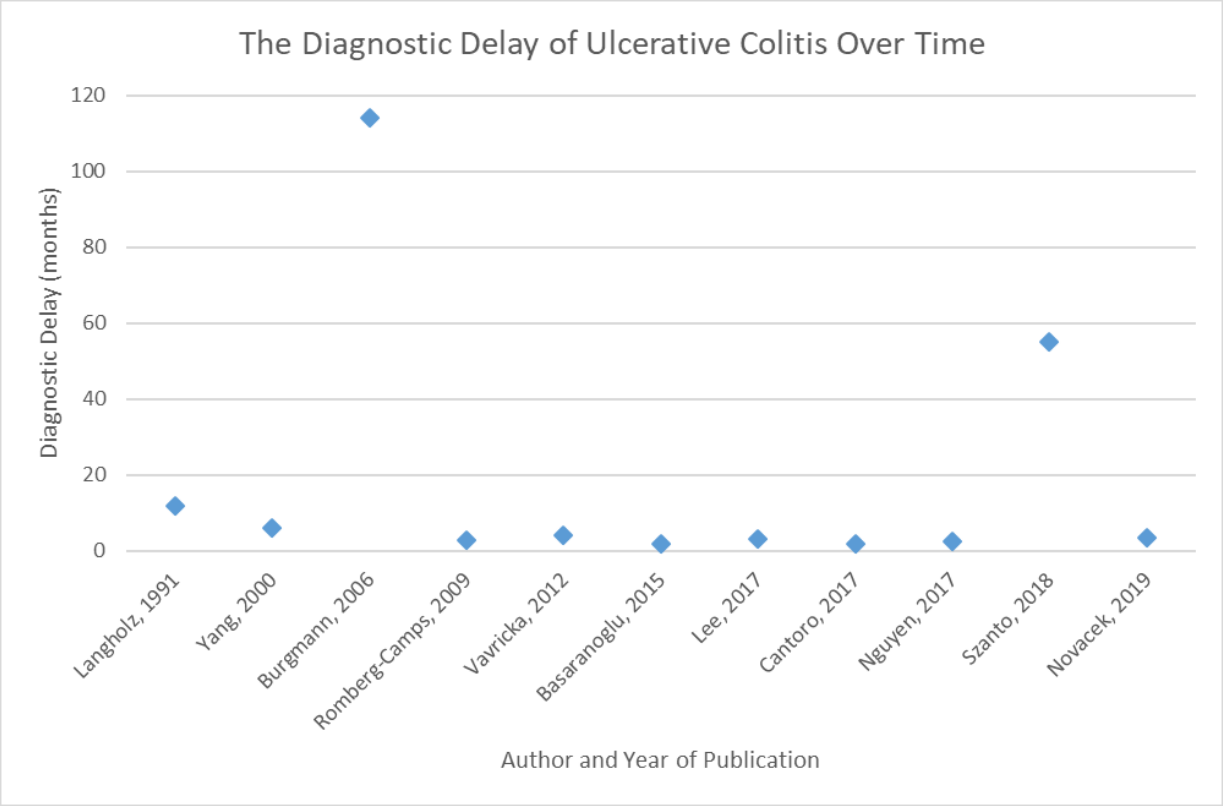


Figure 3.3.3- *A graph showing changes in the extent of diagnostic delay in UC compared to year of publication*

3.3.3.6 Sensitivity analysis

As outlined previously, outliers have been identified during this analysis. The outliers identified include the study by Szanto *et al*. and Burgmann *et al*. With the inclusion of outliers, the median diagnostic delay ranged from 2 months to 96 months for IBD, 2 to 84 months for CD and 2 to 114 months for UC. Following the exclusion of outliers, these ranges change, becoming 2 to 5.3 months for IBD, 2 to 26.4 months for CD and 2 to 12 months for UC. When comparing the delays for CD and UC, CD demonstrates longer diagnostic delays than UC following exclusion of the outliers. **Figure 3.3.4** and **Figure 3.3.5** demonstrate the changes in CD and UC diagnostic delay respectively over time.

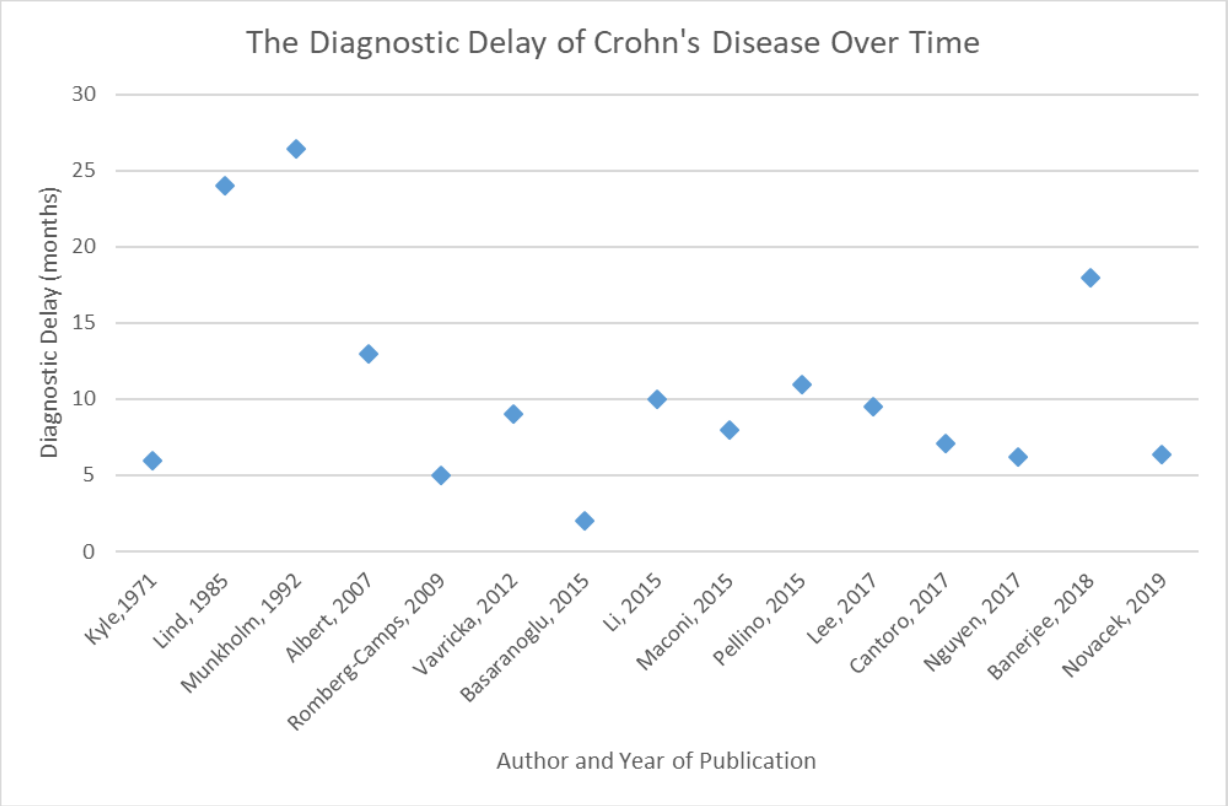


Figure 3.3.4- *A graph showing changes in the extent of diagnostic delay in CD compared to year of publication, following exclusion of outliers*

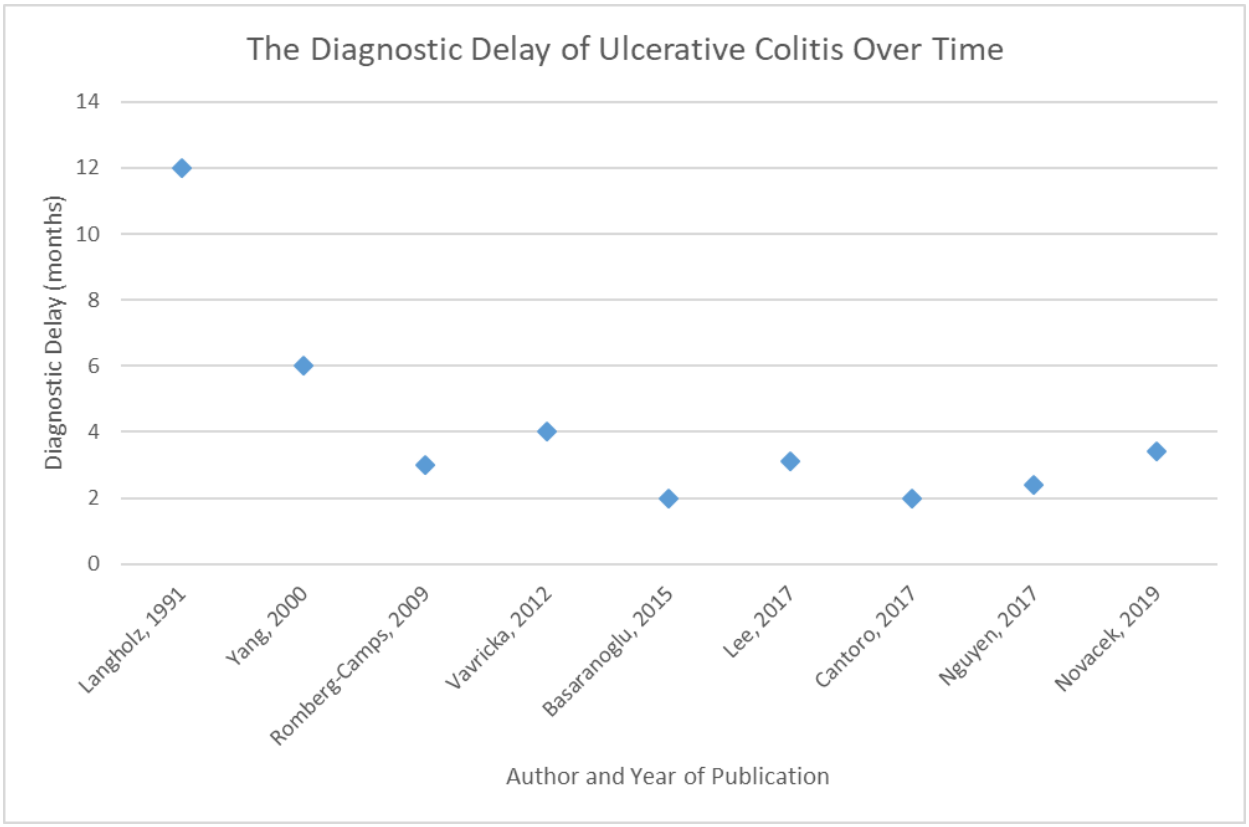


Figure 3.3.5- *A graph showing changes in the extent of diagnostic delay in UC compared to year of publication, following exclusion of outliers*

3.3.3.7 Consultation and Healthcare Delays

Of the thirty-five papers, there were four (11%) that provided information on the extent of diagnostic delay of CD and UC which was attributed to consultation and healthcare delay (**Table 3.3.9**). There was one cross-sectional study (25%) and three retrospective cohort (75%) studies from population data-sets (n= 2, 50%), secondary care (n= 1, 25%) and tertiary care (n= 1, 25%). Two arose from European countries (50%), one from Asia (25%) and one from North America (25%). With regards to the four articles providing this information for CD, three papers demonstrated greater consultation delays compared to healthcare delays. Median consultation delay ranged from 1 (IQR 0.2-4.9) to 2 (IQR 0-6) months whereas healthcare delays were between 0.7 (IQR 0.1-4.6) to 6 months. A similar pattern was not found for UC, as described in three papers where consultation delays were longer, shorter and equal to healthcare delays. Median consultation delays ranged from 0.7 (IQR 0.3-3.0) to 1.9 (IQR 0.9-4.9) months and for healthcare delays, this range was 0.2 (IQR 0.1-0.6) to 1.1 (IQR 0.4-5.4) months. In addition to the four articles described, Cantoro *et al*. provided mean values of consultation and healthcare delays for a sub-cohort of 558 IBD patients, which were 10.8 (SD 30) and 3.1 (SD 12) respectively.

Table 3.3.9- *Data for consultation and healthcare delay, from shortest consultation delay to longest*

				Consultation Delay (months)		**Healthcare Delay (months)**	
Author and Publication Year	**Country**	**Definition of Consultation Delay**	**Definition of Healthcare Delay**	**CD**	**UC**	**CD**	**UC**
Nguyen, 2017	USA	Time from symptom onset to initial physician visit	Initial physician visit to IBD diagnosis	1 (0.2 – 4.9) median (IQR)	0.7 (0.3 – 3.0) median (IQR)	3.5 (1.2 – 20.5) median (IQR)	1.1 (0.4 – 5.4) median (IQR)
Lee, 2017	South Korea	From first symptoms to physician visit	Physician visit to diagnosis	1.9 (0.6 – 8.5)- median (IQR)	1.9 (0.9 – 4.9) median (IQR)	0.7 (0.1 – 4.6) median (IQR)	0.2 (0.1 – 0.6) median (IQR)
Vavricka, 2012	Switzerland	Time from first symptoms to physician visit	Time from physician visit to IBD diagnosis	2 (0 – 6)- median (IQR)	1 (0 – 4)- median (IQR)	4 (0 – 18)- median (IQR)	1 (0 – 5- median (IQR)
Albert, 2007	Germany	First complaints to first consultation	First consultation of doctor to establishment of diagnosis	2 (0 – 171)- median (range) 8.6 (2.1)- mean (SD)		6 (0 – 207)- median (range) 20.8 (38)- mean (SD)	

Key: IBD; Inflammatory Bowel Disease, CD; Crohn's Disease, UC; Ulcerative Colitis, IQR; Interquartile range, SD; Standard deviation

3.3.4 Subgroup analysis

3.3.4.1 Subgroup analysis- age and diagnostic delay

There were three papers that explored diagnostic delay according to age at diagnosis, though only one reported median data. In all of these papers, an older age at symptom onset or diagnosis was linked to diagnostic delay. For instance, one study compared CD diagnosis after the age of 60 years old against individuals with a mean age of 27 years old at diagnosis and found that the median diagnostic delay for both cohorts was 16 and 5 months respectively (Foxworthy, & Wilson, 1985).

3.3.4.2 Sub-group analysis- Western and Eastern Europe

A prospective cohort study by Burisch *et al*. across European countries grouped into Western (n= 14) or Eastern (n= 8) Europe found that diagnostic delay was longer in Western European countries. Of the Western countries, there was a total of 430 patients with CD and 668 with UC. There were 105 patients with CD and 145 with UC across the Eastern European countries. Median values for Western and European countries were 4.6 and 3.4 months respectively for CD and 2.5 and 2.2 months for UC (Burisch, 2014).

3.4 Systematic review discussion

This systematic review examined the extent to which a diagnosis for IBD is, on average, delayed. This work found that overall diagnostic delay continues to be a substantial problem for patients with IBD, though the extent of this does vary between the two main subtypes of IBD, Crohn's disease (CD) and Ulcerative Colitis (UC). Patients with UC are experiencing less delay in receiving their diagnosis than patients with CD, particularly as delays in UC diagnosis seem to have decreased over the last five decades, whereas this is less clear for CD. Additionally, patient-related (consultation) and clinician-related (healthcare) delay is similar in patients with UC. This is in contrast to CD, where delay predominantly occurs once the patient has entered the healthcare system. Following a sensitivity analysis, there was a difference in the spread of median delay, demonstrating that outliers appear to impact on the findings of the systematic review.

Following sensitivity analysis, the median delay in IBD diagnosis was found to range from 2 to 5.3 months. For CD and UC, delay ranged from approximately 2 months to 2 years and 2 months to 1 year respectively. Where articles had directly compared the delay between CD and UC, delay in CD was generally longer than UC delays. Systematic reviews have been conducted into the delay in diagnosis of many medical conditions, including gynaecological cancers, myeloma, giant cell arteritis and tuberculosis (Getnet, Demissie, Assefa, Mengistie, & Worku, 2017; Koshiaris *et al*., 2018; Prior *et al*., 2017; Williams, Murchie, & Bond, 2019). Possible reasons for protracted delays in CD may include diagnostic uncertainty from varied presenting symptoms (Gallinger, Ungaro, Colombel, Sandler, & Chen, 2019). This could be because CD can affect any part of the GI tract whereas only the large bowel is affected in UC (Xavier & Podolsky, 2007). Similarly, the type of symptoms may contribute to diagnostic delays, as it could be assumed that symptoms like rectal bleeding would encourage someone to seek medical advice, a symptom which is more common in UC (Novacek et al., 2019). There is an increased incidence of EIM in CD, approximately 25% as opposed to 10-20% in UC, which could also delay diagnosis (Ephgrave, 2007; Magro *et al.*, 2017;

Vavricka *et al*., 2015). Delays in diagnosis may be protracted in CD as overlapping symptoms may mean in some cases it is initially misdiagnosed as UC (Munkholm *et al.*, 1992).

The findings from the comparison of consultation and healthcare delay demonstrate that the identification of IBD is still problematic, particularly in CD where delays were longer following the patient entering the healthcare system. This could be due to many factors, including the absence of a gold-standard diagnostic test, focussing on the most likely diagnosis and inadequate education of the condition meaning that appropriate investigations are not requested. Consultation delays were mostly found to be between 0 to 2 months, which may have been due to vague symptoms or patient perseverance with symptoms before seeking medical help (Moore, Grime, Campbell, & Richardson, 2013). Systematic reviews of diagnostic delay of other medical conditions have also explored participant (consultation) and clinician-led (healthcare) factors for delay. For instance, a systematic review into the delays in diagnosis of myeloma also reported data on consultation and healthcare delays. Similar to the findings for CD, consultation delays were shorter to healthcare delays, with a median consultation delay of one month and median delay of 108 days following presentation (Koshiaris et al., 2018). The same pattern was also found in a systematic review on the delays in diagnosis of colorectal cancer, where median patient delay ranged from seven days to five months and practitioner delay from zero to fifteen months (Mitchell, Macdonald, Campbell, Weller, & Macleod, 2008). This systematic review exploring colorectal cancer also provided potential causative factors for patient and healthcare delays. Patient delays were linked with patient interpretation of symptoms, awareness of symptoms and knowledge about screening availability; and fear of cancer was seen to both delay and expedite presentation to healthcare services. Attributing symptoms to other medical conditions, negative test results and failure to examine the patient were examples of healthcare delays (Mitchell *et al*., 2008). Interviews with GPs in South Australia found that most were only seeing up to five patients with IBD per month and some GPs uncomfortable with IBD management (Tan, Holloway, Lange, & Andrews, 2012). The reduced exposure of GPs to IBD could explain the protracted healthcare delays. Possible factors

contributing to consultation and healthcare delays, from the participant's perspectives, are explored further in the qualitative research presented in Chapter 4. Certain cognitive processes which may lead to diagnostic delay were discussed by twenty-five GPs in a qualitative study by Balla, Heneghan, Goyder and Thompson. The GPs interviewed proposed that diagnostic errors could occur when failing to consider red flags, ignoring the possibility of a serious disease with low probability and using a previous diagnosis to explain current symptoms (Balla, Heneghan, Goyder, & Thompson, 2012).

The overall diagnostic delay experienced by patients has remained relatively consistent over the last 48 years, implying that there are still limitations in the prompt diagnosis of IBD. The diagnosis of IBD is dependent on the assimilation of results from many investigations, like blood tests, faecal calprotectin, endoscopy and histology. Although the absence of a single, simple investigation to diagnose IBD is likely to make diagnosis more challenging, it would be logical to consider that recent advancements in diagnostics, particularly the introduction of the faecal calprotectin test, would have reduced the interval to IBD diagnosis. Raised faecal calprotectin levels indicate GI inflammation and is used to diagnose and monitor IBD. It is recommended by NICE (2013) that levels should support clinicians in diagnosing IBD and IBS. Therefore, any abnormal faecal calprotectin levels should prompt referral for a diagnosis of IBD and reduce diagnostic delays. However, this review is unlikely to have captured this because patient recruitment period for included articles ended in 2015, and as the faecal calprotectin test was introduced into the NHS in 2013, it may not have been as commonly used (NICE, 2013).

Studies providing diagnostic delay data ranged from 'Westernised' countries including Denmark, the UK, Italy and France as well as from less affluent countries such as Iran and India. There appeared to be no discernible differences in diagnostic delay between these countries despite disparate access to healthcare across these territories. Certain factors may have been linked with longer delays in developing countries, including reduced availability of medical equipment, for

example. However, similarities in delay data suggest this is not an issue. Even if there was a risk of abdominal tuberculosis impacting on diagnostic delay in endemic countries, similar delays were seen in non-endemic countries. The incidence of IBD is increasing in countries that were previously less affected (Ray, 2016; Thia *et al*., 2008), therefore there is a need to improve the diagnosis of IBD in such countries, but an attempt to reduce delay above and beyond that of westernised countries may not be pivotal.

From the sub-group analysis, an older age at symptom onset could contribute to the delays of IBD diagnosis. Reasons for this are largely unclear, although certain abdominal pathology, such as diverticular disease, becomes more common with increasing age and may obscure the IBD diagnosis (Gisbert & Chaparro, 2014). Additionally diagnosis amongst older people may be more challenging as they are more likely to have other health co-morbidities and the presence of cognitive impairment can make obtaining a clear history difficult (van Duin, 2011). These prolonged delays suggest the need to improve the identification of IBD in the older population. In the UK, identification of IBD in older people may also be facilitated by the introduction of screening programs for colorectal cancer, which could uncover asymptomatic or mild IBD. Current NHS screening programs for colorectal cancer include a screening sigmoidoscopy at the age of 55 and faecal immunochemical testing (Gov.uk, 2017). This detects levels of human globin from haemaglobin in faeces, and has replaced the faecal occult blood test that detects haem, which is not as specific at identifying human blood in stool. Further research into the reasons for delays in IBD diagnosis in the older population is needed in order to identify improvements in detection.

3.4.1 Strengths and limitations

This systematic review has successfully condensed and appraised the data from multiple articles within a single paper, providing the reader with a comprehensive overview of the diagnostic delays in IBD reported within the literature.

As discussed previously, there is a risk of bias when conducting a systematic review, therefore a comprehensive protocol was devised and followed before the systematic review was commenced. This protocol was also registered with PROSPERO, to ensure that the method for the review was followed and that duplication of the review by other researchers did not occur.

The use of the PICOS framework for inclusion and exclusion criteria ensured that sufficient consideration of all aspects of these criteria, from a population and study design level, were clear enough to all reviewers. This reduced the risk of bias which may be introduced if reviewers have to rely on their previous knowledge of the subject matter if the criteria is ambiguous. Every effort was made to ensure the inclusion of foreign language articles, as they were only excluded in the absence of a translator to conduct the review and extraction. This is in contrast to other systematic reviews where foreign articles are excluded without attempts at translation (Davis *et al.*, 2015; Rispo *et al*., 2018).

Another strength of this systematic review is the choice of databases used to source articles. A wide geographical area was covered by selecting an American- and European-based database. Similarly, research from a wide range of specialties was ensured, as MEDLINE provides life sciences and biomedical literature, EMBASE offers pharmacological literature and CINAHL contains literature about nursing and allied health professionals.

The volume of literature found from the search is a key strength. Amongst the thirty-five articles included, there were a total of 14,524 participants. In addition, these studies were conducted across a broad geographical area and based in many healthcare settings, largely secondary and

tertiary care. As such, the findings of this systematic review are relevant across many countries with differing healthcare settings.

One key limitation of the systematic review was the exclusion of paediatric literature. Whilst the decision was justified due to time constraints in which to complete the research, IBD is a condition that is common in children and it would be important to explore delays in diagnosis of paediatric IBD.

Another limitation is the process by which titles were reviewed. Due to time constraints, both reviewers (EC and JP) reviewed 50% or the articles by title, which could have led to the accidental exclusion of relevant titles due to human error. The likelihood of this happening from the abstract review stage was reduced, as second reviews were conducted for both abstract and full-text screening.

Although there are similarities between the NOS adaptations for cohort and cross-sectional studies, as they identically assess the representativeness of the sample compared with the target population and both provide evidence of assessing the ascertainment of exposure, there are differences in the scoring systems. For instance, the items used to assess outcome contains identical statements, however the number of stars awarded varies, as in the cohort NOS independent blind assessment or record linkage are awarded one star each and self-report is not awarded stars. In the cross-sectional NOS, blind assessment and record linkage are awarded two stars each and self-report is awarded one star. The variation between the NOS scale for cohort and cross-sectional studies reduces comparability of quality between the two study designs.

3.4.2 Conclusion

The findings of this systematic review demonstrate that the diagnostic delay of IBD remains an important issue to rectify, particularly as reductions in diagnostic delay were only seen in UC. As

demonstrated in the findings for consultation and healthcare delay, improvements must be made in the identification of IBD, particularly amongst healthcare professionals.

*3.4.3**Chapter summary***

Alongside the completion of this systematic review, interviews were conducted with patients who have experienced delays in IBD diagnosis may be able to shed light on where problems in the diagnostic pathway of IBD lie. A convergent mixed method design is demonstrated by the combination of findings from both the systematic review and qualitative research, which are presented together in Chapter 6.

4 Reasons for Diagnostic Delay in Inflammatory Bowel Disease- Qualitative Research

A qualitative approach was adopted to answer the specific research objective outlined in Chapter 1, section 1.3, which was to explore possible reasons for, and consequences of, diagnostic delay, from the perspective of individuals who have experienced a delay in Inflammatory Bowel Disease (IBD) diagnosis. Qualitative methods have previously been used to explore the reasons for diagnostic delay in other conditions. For example, semi-structured interviews were conducted by Liddle et al. (2015) with UK participants following their experiences of gout from symptom onset to diagnosis. Confusion over symptoms, self-diagnosis or self-medication were cited by participants as being patient-level factors contributing to delay, whereas atypical presentation of gout and female gender were perceived healthcare factors for delay. Using similar methods to explore the experiences of individuals with IBD may lead to the identification of common contributing factors for delay in diagnosis across different conditions, as well as factors that are specific to IBD; and will also allow for investigation of the perceived impact of diagnostic delay on the clinical course of IBD.

4.1 An overview of the qualitative research conducted in this thesis

Qualitative research is generally concerned with formulating an in-depth understanding of a topic across a variety of dimensions. This research aimed to obtain accounts from patients about their opinions towards their delayed diagnosis, so adopting a qualitative approach enabled an understanding of how participants process and interpret their experiences, as well as demonstrating how personal circumstances can impact on these experiences. In particular, the use of semi-structured telephone interviews in this study allowed for flexibility so that the participant could set the agenda and expand on areas within their experience deemed significant or important to them (Almeida, Faria, & Queirós, 2017). This has been outlined in further detail in section 4.6.

Where the systematic review presented in the last chapter gave a benchmark value of diagnostic delay, establishing that delays in IBD are a pertinent issue, the qualitative study builds upon this and provides further context, through identifying possible causative factors and consequences of delay. As described in Chapter 1, section 1.4, a pragmatic methodological approach was adopted as the choice of research methods were selected based upon fulfilling the aims of the research (Brierley, 2017).

4.2 Participant recruitment

Ethical approval for the qualitative research was granted by Keele University's Research Ethics Committee (ERP 2402).

4.2.1 Sampling framework

To ensure the most suitable participants were selected for the qualitative study, the following inclusion and exclusion criteria were applied (**Table 4.2.1**). In order to sample from an appropriate population, the inclusion threshold of delay of three months was decided. This would ensure inclusion of people with a comparatively small delay and reduce the risk of bias by only selecting people who had protracted delays, as such individuals may have a worse disease course. This decision was influenced by a study in which the median delay of diagnosis for IBD was three months (Cantoro et al., 2017). As the systematic review pertained to adult diagnostic delay, participants of 18 years or older were invited to participate to ensure comparability of the systematic review and qualitative research findings.

Table 4.2.1- Inclusion and exclusion criteria for participant selection

Inclusion Criteria	Exclusion Criteria
• Over 18 years old • Diagnosis of IBD, specifically CD or UC • Can communicate in English • Diagnostic delay of more than 3 months • NHS treatment (previously or ongoing)	• Younger than 18 years old • Diagnosis of indeterminate colitis • Unable to communicate in English • Diagnosis within 3 months • Have not received previous/current treatment from the NHS

4.3 Sampling and recruitment

Recruitment took place between 31st October 2018 and 23rd January 2019 by posting on social media and advertising the study at an event hosted by Crohn's and Colitis UK (C&CUK) in the Midlands, UK. C&CUK are a nationwide charity supporting people with IBD (Crohn's and Colitis UK). There are branches across the UK that organise events to increase awareness and support those living with IBD. The C&CUK website provides information about IBD for the general population and healthcare professionals, avenues of support, advertising research and fundraising.

A poster was created which contained an overview of the study and contact details for the research team, which was used to recruit through social media (**Appendix 6**).

4.3.1 The use of convenience sampling

Convenience sampling involves recruiting participants into a study based on accessibility or proximity to the research (Etikan, Musa, & Alkassim, 2016). Eligible individuals that responded to

the study advertisements and subsequently agreed to take part in an interview were recruited. The decision to adopt this sampling method focused around time constraints in which to complete the research. It is important to acknowledge that the nature of convenience sampling means it is more difficult to control the characteristics of the participants who volunteer for the study (Smith & Noble, 2014). Although eligibility for the study was ensured by distributing the inclusion and exclusion criteria to participants, the extent of their delay was not disclosed before the interviews were conducted, meaning that there was a risk of a reduced range of delay from the sampled participants. Similarly, participant demographics including age and gender were unable to be controlled for, besides confirming that the participant was over 18 years old and eligible to participate in the study.

4.3.2 Avenues of recruitment

The decision to recruit through social media was made as it allowed access to a large, geographically dispersed population from which to recruit participants. With increasing popularity of social media, it is considered an effective means of recruitment to research (Frandsen, Walters, & Ferguson, 2014; Gelinas et al., 2017; Yuan, Bare, Johnson, & Saberi, 2014). Social media can be an avenue of support to people with a multitude of health and social issues (Patel, Chang, Greysen, & Chopra, 2015) including IBD, therefore this is a useful method to access individuals who engage in online support groups, and who may be willing to participate in research. In addition, the study was advertised on the Crohn's and Colitis UK (C&CUK) website, in the 'take part in research' section.

4.3.2.1 Twitter

A Twitter account (@IBDresearchKLE) was created to produce public tweets advertising the study using the poster described in section 4.3 (**Appendix 6**). From 31st October to 21st December 2018, 12 tweets advertising the study were posted, which were retweeted 62 times and 'liked' 54 times. 'Retweeting' these tweets was encouraged so my posts could extend information of this study into social media user feeds. I also used 'hashtags' within recruitment tweets, which act as a label and group them with other tweets bearing the same hashtag, again potentially allowing access to a wider audience (Shapp, 2014). Examples of hashtags used in advertising tweets included #IBD, #crohnsdisease and #ulcerativecolitis.

4.3.2.2 Facebook

I also recruited participants by uploading a status advertising the study to my personal Facebook account. This post was shared by 26 Facebook users allowing their Facebook contacts to see this status. A Facebook group run by Keele University for students was also utilised as a platform for recruitment, with one post uploaded to this group which could be viewed by all members.

4.3.2.3 Crohn's and Colitis UK

On 25th November 2018, I advertised the research to guests attending an event hosted by the North Midlands branch of the national charity C&CUK. The existing knowledge of delays in diagnosis, as well some literature discussing the impact of this delayed diagnosis, was presented. Despite the small geographical scope, individuals were recruited who may not have been accessible through social media. The study was also advertised on the C&CUK website. C&CUK are nationally recognised in so the support from this charity was invaluable in giving credibility to the research. I

provided an email address and telephone number to ensure I could be contacted directly. The website address was also added to tweets sent from @IBDresearchKLE to allow people to find out more about the study.

4.3.3 ***Participant correspondence***

After they had made initial contact expressing interest in the study, the contact details of potential participants were obtained depending on the individual's preferred means of contact. All of those who expressed an initial interest in participating in the study agreed to be contacted by email. Prospective participants were contacted using a generic email that outlined the study aims and the inclusion criteria for the study. A participant cover letter, information sheet and consent form (**Appendix 7** to **Appendix 9**) were attached to this email and those who met the inclusion criteria were asked to read these documents and complete the consent form. If the participant did not fulfil the criteria outlined in the email, they were thanked for their interest but informed that they would not be included in the study.

The participant information sheet provided a further overview of the study, how participant data would be used, the potential risks and benefits of taking part and steps participants can take if they choose to withdraw from the research. Eligible participants were asked to return the completed consent form either by email or post. Upon receipt of the consent form, the participant was contacted by email or telephone to arrange a convenient date and time to conduct the telephone interview and asked to provide a contact number.

4.4 <u>The interview process</u>

Interviews were conducted between the 5th December 2018 and the 7th February 2019.

4.4.1 Topic guide

A topic guide was developed based on the research aims and existing literature (Kallio, Pietilä, Johnson, & Kangasniemi, 2016). This guide was used as an aide memoire to steer the interview proceedings. I decided against restricting myself to following the guide rigidly as I wanted to maintain an inductive approach through the data collection and this may have provided too much structure for my semi-structured interviews.

The topic guide was split into six sections to explore different aspects the participant's experience of diagnostic delay (Appendix 10). The topic guide was iteratively revised throughout the interview process based on emergent findings. For instance, in an early interview one participant explicitly talked about their emotional reaction to delayed diagnosis, and this was something I explored further in subsequent interviews. On the other hand, asking participants about the time taken to get a GP appointment was removed from the topic guide as for some individuals their diagnosis was many years ago and they could not recall this information accurately. Whilst reference to participant and healthcare factors for delay was initially included in the topic guide, I decided to expand on this, by asking specifically about GP and hospital delays, as a result of the preliminary analysis of literature included in the systematic review that has previously explored this concept.

4.4.2 Telephone interviews

I chose to use telephone interviews as they are an established means of collecting qualitative data and allowed for the inclusion of people with IBD across a broader geographical area within the UK, within a shorter time period (Novick, 2008).

Prior to conducting the interviews, I was mindful of the challenges that can arise when building rapport during telephone conversations. I was aware that I would be asking participants about possibly sensitive or personal issues, therefore I wanted to put them at ease so they would be

comfortable discussing this information. I decided to have a brief conversation with the participant before commencing the interview, as opposed to beginning the interview questioning straightaway. All participants were open and willing to share their accounts therefore the telephone was not a barrier to the interview process.

Each interview was recorded on an Olympus WS-6505 recorder to ensure clear sound quality for transcription.

4.4.3 An outline of the interviews

When the participant answered the phone, I confirmed my identity and checked that they were available for the interview. I decided to present myself as a researcher who had taken a year away from my medical studies to participants. I questioned whether knowing I was a medical student from the start would influence how they answered my questions, as they may assume I am knowledgeable in IBD. I wanted participants to fully explain their accounts and not allow my knowledge of the subject influence their responses.

Participants were then asked to confirm their consent to be involved in the study and I checked that they were happy for the interview to be recorded. Though this information was included in the participant information sheet, I decided that each participant should reaffirm consent before the interview began. For one participant who requested to provide consent over the phone, the consent form was read out and they then gave me permission to complete and countersign the form. As this participant was unable provide signed consent, this conversation was audio-recorded.

I aimed to achieve an understanding of the participants' overall journey to diagnosis including impact of a delayed diagnosis and factors they thought could have contributed to their delay. Where I sensed that participants were not forthcoming in providing information, such as when they expressed concern that their responses were not relevant to the research, I would use open

questioning to encourage participants to consider their responses, including *"can you tell me a little bit more about..."* and *"how else do you think…"*. I wanted to empower the individual to discuss matters deemed important to them and dissolve any perceived power-imbalance they may feel exists in this researcher-participant interaction. I also did this by reiterating my gratitude to the participant for their involvement in the study and that their help in this research would improve understanding of diagnostic delays in IBD. This demonstrated to the participant my desire to include them as a collaborator in the research (Mishler, 1986).

The interview concluded with a brief summary of the conversation to allow any final questions or areas of discussion to be raised by the participant or myself. Again, consent to participate in the research was checked. The participant was thanked for their contribution to the study and asked if they would like to receive a summary of research findings at the end of the study. All participants expressed an interest in receiving information regarding the research outcomes.

4.4.4 Note-taking

Brief notes were taken during the interviews as a reminder of interesting points to discuss further. I felt that taking short notes enhanced the semi-structured nature of the interviews as it reminded me to return to points that the participant deemed significant. For this reason, it was advantageous that interviews were conducted over the phone rather than in face-to-face interviews, as I was concerned participants may feel uncomfortable if they were watching me take notes. Participants were told that I would be taking short notes during the interview to signpost the interview, which they consented to and note-taking was done concisely and unobtrusively during the interview. These notes, which were only single words or short phrases used as cues to guide conversation, were subsequently destroyed as I felt they would not contribute to the analysis phase as all relevant information was included within the transcripts.

4.5 Data storage

Achieving a balance between protecting participant anonymity whilst simultaneously maintaining the richness of the data for analysis can be complex and it is important to acknowledge that anonymity cannot always be guaranteed when managing interview data, however steps were taken reduced this risk (Saunders, Kitzinger, & Kitzinger, 2014). All documents containing participant information were stored on a secure drive that only the research team could access. Paper copies of consent forms were printed and stored in a locked drawer. Once each interview was completed, the recording was uploaded to this drive. Each participant was assigned a number, all identifiable information such as names of clinicians and hospitals was removed from the transcripts and participants' real names were replaced with pseudonyms.

4.6 Interview transcription

I transcribed six interviews in full, which was an important learning opportunity and also allowed for full immersion into the data, which is discussed below. Due to limited time in which to complete the research, the remaining 10 recordings were transcribed using a transcription company with a confidentiality agreement in place (The Transcription Company). Whilst all interview content was transcribed, extra-linguistic features such as pauses, 'erm' et cetera, were omitted as they were not considered pertinent to the data analysis.

4.7 Data saturation

Data collection ceased when data saturation was perceived to have been achieved. I adopted an inductive definition to saturation, where data collection was stopped when novel codes were no longer arising from the data during analysis (Saunders et al., 2018; Urquhart, 2012). Assessing

saturation from the coding stage was possible as data collection and data analysis occurred in parallel.

4.8 Data analysis

Data were analysed using thematic analysis. Thematic analysis is a method for identifying, analysing, and reporting patterns (themes) within data (Braun & Clarke, 2006). The decision to use thematic analysis was based on the advantages of flexibility when creating and assimilating codes. Thematic analysis also allows the ability to draw comparisons of key concepts arising across the data and between participant experiences (Braun & Clarke, 2006). I believed that developing broad themes that combined key findings from accounts from multiple participants provided a stronger insight into patient experiences of delay rather than focusing just on individual accounts without drawing connections between these.

The thematic analysis was guided by an approach outlined by Braun and Clarke. This approach provides the freedom and flexibility to comprehensively analyse participant data as a collective, whilst providing the structure to ensure that a thorough analysis of the data was completed (Braun & Clarke, 2006). This structure includes guidance on data immersion as well as creating and reviewing codes and themes, which comprise the following sub-headings under which further detail on the analysis is provided. Data collection and analysis were concurrent to allow for reflection and refinement of the interview process as a result of the analysis.

The constant comparative method was adopted when developing codes and assimilating them into themes, which involves evaluating the current coded extract with extracts that have been attributed the same code. This allows the identification and development of certain features or properties within extracts that make up certain codes, allowing the ability to later form themes (Glaser, Strauss, & Strutzel, 1968).

4.8.1 Data Immersion

The first step of thematic analysis involves immersing oneself within the data to increase awareness of content. This was done during the transcription process and by close reading and re-reading of transcripts before coding. This was particularly significant with the transcripts produced by the transcription company, where data immersion occurred alongside quality controlling the returned transcripts by comparing them to the audio recording as well as anonymising and refining transcripts by removing any extra-linguistic features, as described previously. As acknowledged by Braun and Clarke, data immersion is a time-consuming and arduous process but it is invaluable to be familiar with the data (Braun & Clarke, 2006).

The main reason I felt this step was so important was that I was reminded of certain discussions from interviews which was useful when time had lapsed since the interview. By refreshing my memory of the interview, when the time came to code the data I was able to navigate through transcripts efficiently. In addition, I was also able to reflect on my performance as the interviewer during this process and identifying weaknesses in my interview technique, such as asking multiple questions at once or moving away from a topic without exploring it in more depth. I was therefore able to refine my technique for future interviews.

4.8.2 Initial coding

Following data immersion, coding allows meaning to be assigned to key sections of the data depending on the interpretation of the analyst. In this analysis, an inductive or data-driven approach was used to coding, where codes are constructed based on the presented data and not selected from a previously assembled list of codes. This demonstrates a grounded approach, where efforts have been made to prevent the analysis of data being influenced by pre-existing ideas or opinions (Glaser and Strauss, 1967). As proposed by Boyatzis, deductive coding is based on

assumptions that certain principles can be applied to any phenomenon, which moves the researcher away from data-driven coding (Boyatzis, 1998). I was concerned about the risk of being led by pre-selected codes instead of the content of the data. When adopting an inductive approach, I initially coded the data on a line-by-line basis to ensure that I did not omit any valuable data. I made a concerted effort to ensure I adopted this inductive approach and not allow my prior understanding of IBD or healthcare to influence my coding, which is commonly known as 'bracketing' one's own knowledge and assumptions. In practice, interpreting the data without applying my prior knowledge of the subject matter was sometimes challenging and I have explored this further in section 4.11. The qualitative management software used to complete this step of the analysis was Nvivo 12 (version 12.2.0, QSR international). I decided to code the data using Nvivo 12 as there is increased flexibility to change or delete codes. When electronically coding, groups of extracts from different interviews with the same code can be viewed simultaneously, allowing me to quickly see the relevant data for a certain code.

4.8.3 Creating themes

As described by Braun and Clarke, the creation of themes involves looking at the data in a broader sense through analysing each code and combining them based on common meanings (Braun & Clarke, 2006).

As the coding process progressed, I felt that there were key categories that were developing, which were grouped with other categories to eventually form the over-arching themes. My method of generating themes was guided by the constant comparison method, which was previously described (Glaser and Strauss, 1968). If the groups of codes within themes were more clearly connected, these were collated into sub-themes.

4.8.4 Reviewing themes

There are two levels of review that form this part of the analysis, including reviewing the data by codes and then by themes. Reviewing at code-level involves checking whether the interview extracts correspond to the assigned code, whereas reviewing at theme-level analyses whether the themes reflect the broader meanings of the data set (Braun & Clarke, 2006). This may involve refining, merging or excluding the initial themes.

I used Nvivo 12 to review the quality of the coded information as there is a feature which highlights extracts based on their code. I reviewed all transcripts to confirm that my interpretations were sufficiently grounded in the data. The quality of my themes was reviewed through the generation of mind maps (Appendix 11). Using mind maps allowed me to identify emerging themes and any connections between these, which was recommended by Braun and Clarke (2006) and utilised by Lynass, Pykhtina and Cooper (2012) within their research. Emerging themes that I perceived to be strongly related were combined to create the overarching themes presented in the results.

4.9 Ethical considerations

Confidentiality and anonymity was ensured by privately corresponding with participants, using email or private message on Twitter, for example. I ensured that all telephone interviews were conducted in a private room where conversations could not be overheard. Personal details of the participants were stored on a password-protected laptop and the audio files were uploaded to a secure drive and were deleted after being transcribed. The data collected from the interviews was anonymised by omitting locations from transcripts and pseudonyms were used when presenting the findings during data immersion, outlined in section 4.8.1.

It was important to have arrangements in place if participants became distressed or upset. Although the risk to participant mental wellbeing was considered low, a protocol was in place if

needed. Following advice from the university ethics committee, I included contact information that participants could use to access support if necessary, i.e. their GP and NHS 111, or by contacting myself for further guidance. Suitable avenues included the Crohn's and Colitis UK charity or Samaritans. After the interview, participants were signposted to this information in case they felt distressed after the interview. In the event that a participant became emotional during the interview, I planned to pause or terminate the interview, offer verbal support and direct them to appropriate assistance.

4.10 Reflexivity

An important aspect of the research process is the researcher's awareness of how they influence and transform the research. According to Finlay, this influence is not a negative event, rather it is a by-product of the researcher's interaction with the research, though it should be acknowledged and described where possible to allow the reader to view the data through the eyes of the researcher (Finlay, 2002).

When regarding my own reflexivity, I believe that my role in healthcare is important to discuss. For instance, the role of a training doctor is to identify the disease from the presenting symptoms, therefore I was concerned I would view the patient from a biomedical perspective without fully exploring their thoughts and feelings. When interviewing, I found this was not an issue as the semi-structured interviews were flexible and void of time constraints, which is very different to the common time-pressured scenario in clinical medicine that I have had to adapt to.

I was aware that I may influence the collection of data through my experiences as a medical student as I may have tried to justify the actions of the GPs and specialists discussed in the interviews as opposed to appreciating and accepting what the participant has described, particularly where negative experiences of healthcare were described. This was because of my

appreciation of certain pathways and thought processes that occur behind the scenes in clinical practice that the patient may be unaware of. However, my clinical experience as a student has also taught me that clinicians may not always acknowledge the perspective of the patient, and as these interviews focused on the patient experience of delay, therefore I avoided making assumptions. In practice, adopting an inductive approach to data collection and analysis can be difficult, particularly with my knowledge of IBD and experience of healthcare, therefore I challenged any assumptions I made during this process and focussed on the experience of the patient as opposed to my own opinions.

Primarily identifying myself to participants as a researcher as opposed to a medical student proved to be a more effective approach. I had considered the participants' expectations of my knowledge and also that my position as a student may influence their interaction with myself. For instance, they may assume that I am more focused on their medical history as opposed to their viewpoints and opinions and as many participants described feeling that their doctor did not want to spend the time discussing their symptoms, I did not want this to project onto our interview. However, I felt that I asked many open questions and focused on participant thoughts and opinions besides their medical history, therefore for participants that were aware of my medical background, this was not an issue.

4.11 Chapter summary

A semi-structured approach to interviewing was utilised to gain insight into participants' experiences of diagnostic delay in IBD. Participants were recruited through social media and a local IBD charity event in order to maintain voluntary involvement in the study. Thematic analysis was used to analyse the data, which involved the generation of codes that were aggregated into overriding themes. The following chapter outlines the findings of this research.

5 Qualitative Findings

This chapter outlines the findings from the patient interviews. As discussed in Chapter 4, the data were analysed using thematic analysis. Three key themes, and sub-themes, were developed from the analysis which are labelled as such:

1) Misdiagnoses
2) Contributors to Delay
    - Participant factors for delay
    - Primary care factors for delay
    - Systemic factors for delay
3) Consequences of Delay

In what follows, the characteristics of the participant sample will first be outlined, before reporting on the findings in relation to each of these three key themes, in turn.

5.1 Participant Demographics

Sixteen participants were interviewed, out of twenty-seven individuals who expressed interested in partaking in the study. Of those who did not participate, most failed to return a signed consent form, whilst three made contact after saturation had been reached. Six participants (38%) were recruited from the Crohn's and Colitis UK (C&CUK) event, six (38%) were recruited from *Twitter* and four (25%) from *Facebook*, with one of these individuals (6%) being recruited from the Keele University *Facebook* post. Ten females were interviewed (63%). The mean age of participants was 41 years old with a range of 20 to 65 years. The mean age of symptom onset as cited by participants was 20 years old, ranging from early childhood to 50 years old. Mean age at diagnosis of Inflammatory Bowel Disease (IBD) was 29 years, range 15-60 years. Median diagnostic delay was

six years. Four participants were diagnosed with Ulcerative Colitis (UC), 11 with Crohn's Disease (CD) and one female participant described being diagnosed with both UC of the large bowel and CD of the small bowel. Further information about the participants can be found in **Table 5.1.1.**

Table 5.1.1- *Demographic information of the participants included in the study*

Pseudonym	Gender	IBD Phenotype	Occupation	Age Symptoms Began	Age at Diagnosis	Diagnostic Delay	Current Age
Helen	Female	UC	Healthcare	40	40	<1 year	53
Joanne	Female	UC	Healthcare	16	30	14 years	34
Derrick	Male	UC	Professor	8	10	2 years	62
Josie	Female	UC	Student	12	16	4 years	18
Charlotte	Female	UC and CD	Student	14	15	1 year	28
Darren	Male	CD	Student	9	17	8 years	25
Jess	Female	CD	Unemployed	16	23	17 years	38
Sandra	Female	CD	Retired	50	60	10 years	65
Brian	Male	CD	Retired	Early childhood	50	50 years	57
Pamela	Female	CD	Teacher	25	26	1 year	45
Alicia	Female	CD	Office Work	16	19	3 years	22
Emily	Female	CD	Office Work	10	18	8 years	20
Callum	Male	CD	Healthcare	19	20	1 year	23
Lauren	Female	CD	Unemployed	16	42	26 years	45
Simon	Male	CD	Retired	36	47	11 years	65
John	Male	CD	Retired	29	31	2 years	56

5.2 Misdiagnoses

This theme refers to participants' accounts of the incorrect diagnoses given to them before being diagnosed with IBD. Also included in this theme is an overview of the presenting symptoms that the participants initially recalled seeking medical advice for. A common feature amongst some participants' diagnostic journeys was initially being diagnosed with gastroenteritis when they presented with recent-onset symptoms, but later being diagnosed with IBS when the same symptoms persisted. This is discussed below.

Irritable Bowel Syndrome (IBS) was cited as a misdiagnosis amongst eight participants. As discussed in Chapter 2, IBS is a common functional disorder of the GI tract. Symptoms include a change in bowel habit and abdominal pain, which can be managed with changes in diet and antispasmodics. (Weaver et al., 2017). IBS is not considered as serious as IBD, though symptoms may still significantly impact on an individual's life.

Participants reported that symptoms of diarrhoea, nausea and abdominal pain were often attributed to gastroenteritis and later IBS by their GP. Some described not having any investigations performed before receiving this diagnosis:

> *I went to my GP at the time, I'm not there now* [i.e. no longer registered at the same GP practice], *and they just said 'ooh you've got a tummy bug' first of all and when it didn't clear up, 'it's probably IBS'. You know slightly different things but not sending me for any exploratory tests or anything. So just sort of saying 'it's probably this, it's probably that' and not really giving me any answers; so that was the initial thing.* *[Jess, 38, CD]*

Participants recalled their GP diagnosing them with IBS due to stressors in their lives, particularly occupational. John recalled how his reports of experiencing stress at work seemed to influence his GP's diagnosis:

> *EC- So do you mind starting off from 29* [i.e. the age of symptom onset]. *What symptoms you were getting at the time?*
>
> *John- Yeah, so diarrhoea, very frequent diarrhoea, probably, trying to think back, some blood in the poo as well, mucus and also general feelings of fatigue, absolutely shattered most of the time, so initially the word IBS was mentioned as I had quite a stressful job but symptoms kept getting worse* *[John, 56- CD]*

A small number of participants remembered being investigated for their symptoms upon presentation, however normal results appeared to confirm a diagnosis of IBS to their GPs. Helen recalled her GP repeatedly sending stool samples for analysis which all came back normal. She later discussed how she felt that her GP thought she would keep presenting which is why he decided to test her stool, suggesting that he did not take her symptoms seriously:

> *Well it was 13 years ago I was 40 when I was diagnosed and I'd gone through an awful lot of stress and I lost a lot of weight through stress I think and I started with what I thought was a bit of a bug or a virus. It started with nothing major, no major issues, but there was a lot of bloating and then it started to get like cramping in my stomach and diarrhoea a lot and I lost more weight so I went to the doctors and eventually after about 3-4 visits to the doctor saying 'look I'm no better' he started to send stool samples away, and every stool sample he sent away came back clear. So he said "I don't really know what we can do it's just IBS you're just going through a period of stress" … I don't think he did really* [interpret her symptoms]*, he just said if it's something you've eaten or a bug it'll go, you know, he initially thought I*

wasn't gonna go away … but all he was giving me then was loperamide [anti-diarrhoeal medication] *which did nothing and he thought it was just IBS through stress really.*

[Helen, 53- UC]

Some participants described being diagnosed with IBS for a long period of time, often years, despite ongoing severe symptoms. Joanne demonstrated an earlier acceptance towards her diagnosis of IBS, implying that she thought at the time it was a plausible explanation for her ongoing symptoms:

"Then I was told it was IBS, so I lived my life without having any actual other tests believing I had IBS for a very, very long time until about four or five years ago, I just became quite unwell" *[Joanne, 34- UC]*

Perceived flaws in the diagnostic pathways used with patients presenting with gastroenterological symptoms was discussed. John argued that the diagnosis of IBS could be an easy explanation on the part of GPs for patients' symptoms. In addition to missing an IBD diagnosis, he describes a similar concern of cancer being misdiagnosed as IBS:

"Yes well all GPs have a pathway don't they? And because a number of things along the lines of IBD can be nicely sort of glossed over as being IBS to start with, probably many people are palmed off with that and I know, I do a lot of volunteering for Bowel Cancer UK, I do a lot of speaking for them and you know the number of people you speak to you who were told they had IBS when they actually had bowel cancer you know, so statistically it's probably not a huge number but it seems to be quite significant. IBS covers thousands of sins and yeah it's IBS, but in others its masking you know something more serious so it's, quite whether there is

a diagnostic tool for GPs to perhaps refer sooner rather than later I don't know…"

[John, 56- CD]

John suggests that the reliance by GPs on IBS as almost being a blanket diagnosis for generic gastroenterological symptoms, could be a barrier to diagnosing *"something more serious",* as in his view, GPs are discouraged from investigating the patient any further.

A diagnosis of haemorrhoids was initially given to two participants. In Sandra's case, she felt like this diagnosis was acceptable as she presented with rectal bleeding:

Sandra- It actually started I think 10 years previously when I was about 50, I got a very tiny amount of blood each morning when I went to the toilet and then, I mean it takes a while to go to the GP, but anyway… I went to the GP and she examined me and she said 'I can't find anything, so it's probably haemorrhoids, use some cream. I used some cream and it didn't have any effect really at all. Sometimes I was ok sometimes I wasn't …

EC- Did you think at that point there was something else going on or did you think that was the correct diagnosis?

Sandra- No, originally I just accepted it. *[Sandra, 65- CD]*

In addition to stress-related IBS, other mental health conditions were cited by participants as misdiagnoses they had received before their IBD diagnosis. As discussed above in relation to IBS, receiving normal tests results seemed to reassure the GP that there was no physical cause to the symptoms, further reinforcing their original diagnosis. Brian recalled being diagnosed with viral or stress-related illnesses before his formal diagnosis of severe depression:

Brian- They'd say to me 'your bloods are normal, it must be psychological, or you've got a virus, here are some antibiotics'. And all this time my body was readjusting

EC- So did they, so you mentioned then 'oh its viral or an infection'

Brian- Yes, prone to viruses … It was the waking up and going to the toilet and I'd say 'so tell me why I keep going to the toilet then?', 'well you know because you're maybe getting stressed and it's coming out on you that way'. There was all sorts… *[Brian, 57- CD]*

Brian reported that his symptoms continued until he was eventually admitted to a psychiatric hospital for 'severe depression' due to extreme fatigue, which in hindsight he felt was a consequence of his undiagnosed CD. However, he reported that at one stage, he did believe that his symptoms may have had psychological causes:

Brian- I saw a consultant, this particular day, she sat there as well and she, it was a conference thing, meetings whatever, and he was asking me to lift my arms up and I had such a job and she said 'he really has got severe depression'

…

EC- Did you at the time feel like you had mental health problems that they were diagnosing you with?

Brian- No, what I mean is, I was convinced in the end that I had [got mental health problems] *because I thought it must be then that I've got something like my mum's got… I think it was Crohn's Org that* [later] *told me it is quite common that these things have happened to people* [prior to their IBD diagnosis]*, you know to be put in a mental institution.*

[Brian, 57- CD]

Derrick, who was diagnosed with IBD at the age of ten, recalled originally being described as a *"nervous child"*, though he attributed this behaviour to the distress at the possibility of experiencing incontinence at school due to his IBD:

> *I was a very nervous child, which is a continual bugbear when people say that I'm sure you're familiar with it. You're nervous because you're running to the toilet, you know desperately not trying to go to the loo in front of everybody. Especially when you're at prep school and you're wearing shorts, it makes my skin crawl thinking about it actually, but that's why you're nervous. So they were thinking that it was my nerves that was causing the diarrhoea, do you see?* *[Derrick, 62-UC]*

One participant recalled how her pre-existing mental health conditions seemed to influence doctors into attributing her gastrointestinal symptoms to psychological factors rather than to IBD. Whilst she was initially told that her GI symptoms were stress-related, the weight loss she subsequently experienced led to her being misdiagnosed with an eating disorder; a diagnosis that she reports not accepting at the time:

> *So from then onwards I was back and forth, back and forth, back and forth* [repeatedly seeing the GP]*, all of those years, again it was "stress, anxiety"… because I've got panic disorder, as soon as I got that label, that was it, and then 2013 I suffered significant weight loss so then the next diagnosis was that I had a borderline eating disorder. I don't know where this came from! The psych team basically went 'oh you are far too thin, you know, this needs to be addressed'. So I saw a dietician once and then I self-discharged from those people because I thought I really don't have an eating disorder, everything they were saying to me, I kept on saying no that's not what happens.* *[Lauren, 45- CD]*

Memories of the emotions felt by participants were discussed when they recounted their misdiagnoses. The frustrations that participants felt during this time about not having a satisfactory diagnosis were compounded by the effect of their symptoms and how unwell they felt:

> *I felt quite annoyed and upset because I was basically being told there was nothing wrong with me when I felt very incredibly ill and I knew there was something wrong, but the doctors were still telling me that there was nothing wrong. So I felt like I wasn't being taken seriously.* *[Josie, 18- UC]*

Brian described concern and worry for his family when he was admitted to the psychiatric hospital for his severe depression:

> *I had every emotion going on, and I was worried about my kids worrying about her* [his wife] *but there was nothing I could do about it because of how poorly I felt as well. You actually, I actually felt like it was gonna be the rest of my life, I actually thought, I actually convinced myself I was never gonna come out* *[Brian, 57- CD]*

5.3 Contributors to Delay

Factors which participants believed led to their delayed diagnosis are discussed within this theme. These factors are divided into three separate subthemes: participant factors, primary care factors and systemic factors.

5.3.1 Sub-theme: participant factors for delay

Participants acknowledged that they may have been, at least in part, responsible for the delay in their diagnosis due to delaying initial help-seeking. Key reasons why participants believed they did

not seek medical advice when symptoms first presented, or why they did not push harder to gain a diagnosis, are discussed below. Within this sub-theme, the trigger for participants to pursue an explanation for their symptoms is also discussed, as when discussing delay with participants, they naturally began to talk about how they overcame certain barriers, which was the first step towards the correct diagnosis.

One participant cited embarrassment as a reason why she did not see her GP sooner. It is important to note that other participants discussed embarrassment as a cause of reluctance to discuss symptoms or IBD with friends, though not necessarily towards seeking help for their symptoms by a doctor. Sandra described waiting *"a couple of months"* before consulting her GP and implied that she was reluctant to discuss her symptoms with her GP:

> *EC- do you think there any factors that you're maybe responsible for as to why you didn't get a quick diagnosis?*
>
> *Sandra- Part of it is because first my symptoms were so minute and weren't really affecting me that much, obviously there's the embarrassment factor because of where the problem is but I was old enough to get over that eventually*
>
> *EC- Do you know the timeframe that it was when symptoms started to when you went to see your GP the first time?*
>
> *Sandra- The first time I'd probably had this tiny bleeding for a couple of months before I thought 'oh, I'd better go'. It was that sort of thing- I think embarrassment is a terrible sort of thing but you do put it off as long as you can and because it didn't seem that important you give yourself all sorts of excuses* *[Sandra, 65- CD]*

For one participant who was diagnosed at 15 years old, she believed her reluctance to discuss her symptoms with her mother contributed to her delayed diagnosis. It was only when she noticed

blood in her stool that she disclosed these symptoms as she appeared to perceive the bleeding as more serious than her abdominal pain:

> *Essentially I wasn't telling people about the pain and stuff that I was getting and if I did, I only ended up telling my mum because the fact that I saw blood and obviously seeing blood as a child is a scary thing so that's the only reason why I told my mum then. But if I had told her that I was getting abdominal pain that was not easing back when I started experiencing symptoms, maybe that would have kind of pushed, maybe I would have been diagnosed before the April time and before she took me back to the GP in the January*
>
> *[Charlotte, 28- UC and CD]*

Another participant described ignoring her symptoms as a reason for not initially consulting, which she perceived as contributing to her delayed diagnosis:

> *"At the beginning of the year I did put it down to just like stress at work, you know, OFSTED* [school inspection at work] *and stuff like that, you know I assumed because I'd never been ill, I'd hardly ever been ill before, I think I thought oh god I've had a burst abscess but now my operation's cleared up, I thought I'd just go back to how I was and I think maybe there is a bit of burying your head in the sand sometimes as well, you know, maybe knowing things aren't quite right but hoping they'd just sort themselves out on their own but it got to the stage when it can't be ignored really, and you felt that was early spring, summertime, when things were getting much worse yeah [Pamela, 45- CD]*

It can be inferred that Pamela is a resilient individual who otherwise considers herself as healthy. It was easy for her to deny and normalise her symptoms by *"burying [her] head in the sand"* and hoping they resolve, particularly in light of her work commitments.

In addition to fear of the cause of symptoms, one participant recalled how his fear of hospitals contributed to his delayed diagnosis. Simon did not follow advice from his GP to attend Accident and Emergency when suffering from severe abdominal pain:

> *Simon- I just don't know what my thinking was at the time, I think it was morbidly afraid of being taken into hospital because I'd never been in hospital or anything and I had a real thing about not going into hospital so I didn't want to particularly, maybe face it*
>
> *EC- Do you think that you've kind of contributed to this delay in diagnosis?*
>
> *Simon- Well I always think it's a 50/50* [half his personal contributors for delay, half healthcare factors]. *I think as a patient I did have; I definitely had some kind of fear about hospitals and having things put down me and basically that was a big, I'm not saying an irrational fear but you know…* *[Simon, 65- CD]*

One participant who had been misdiagnosed with IBS attributed his reluctance to accept stress as a cause of his symptoms as a contributor to his delayed diagnosis. The connection between stress and IBS had been discussed in his GP consultation and it can be inferred that he did not visit his GP as much as he may have done if stress had not been linked to his symptoms.

> *EC- Do you think that you yourself created any barriers that prevented you from being diagnosed early?*
>
> *John- I didn't like the inference that I could be stressed, that stress could be affecting my health so I did sort of rail against that a bit, so I would have mentioned it was a possibility that I didn't like the thought that I had a sort of stress-induced illness at the time*
>
> *[John, 56- CD]*

For those participants who described delaying help-seeking for their symptoms, a worsening of their symptoms, to the point where they could no longer be ignored, triggered them to seek further medical help. Pamela realised she could not ignore her symptoms any longer when they worsened:

> *I was just getting worse, you know and it got to the stage where, you know, I couldn't leave the house and you know I tried to go back to work in the September but I think I barely did a week and it was obvious that wasn't going to work so yeah I think at that stage I was going* [to the GP] *quite a lot and then you know they put me through to the hospital for tests*
>
> *[Pamela, 45- CD]*

As well as the impact of her worsening symptoms on everyday life, another factor that prompted Sandra to consult at this point was her concern that her symptoms were due to bowel cancer:

> *EC- And then it got worse, do you think that was the trigger for you to go and see your GP again?*
>
> *Sandra- When it got really bad it took a couple of days before I went because I just thought 'no, this certainly isn't right' and because I was 60 I automatically assumed I'd got bowel cancer.* *[Sandra, 65- CD]*

There was some variation evident across the dataset, as unlike in the extracts above, not all participants felt that their own actions contributed to the delay in diagnosis:

> *EC- Do you think there are any factors that occurred and your diagnosis was delayed because of you?*

Callum- I'm not the one who will shy away from symptoms and be embarrassed about going to the doctors or whatnot *[Callum, 23- CD]*

5.3.2 Sub-theme: primary care factors for delay

Common primary care delays that participants reported included poor GP engagement with symptoms and delayed referral. Many participants described not feeling that their GP was taking their symptoms seriously. Alicia recalled experiencing longstanding symptoms of abdominal pain, rectal bleeding and constipation and struggled to get a referral from her GP despite being concerned that her symptoms were serious:

Alicia- It got to the point where I just, I worked about five minutes away from the doctor, a five minute walk and every day, well probably once a week, I just used to go down to the doctor and go, 'can you help me, can you refer me?' and they just used to fob me off, peppermint capsules et cetera and I just went every single week for what must have been eight or nine weeks, that's when someone actually referred me so yeah, I must have been to the GP 30 times…

EC- So in what way do you think the doctors that you saw led to you having a delayed diagnosis?

Alicia- I would put most of the blame on the GPs to be honest I think I kind of knew that it was something to do with my bowels that was making me so ill and I basically spelt it out to him that I had virtually all of the symptoms my grandma had [who was diagnosed with CD]'

[Alicia, 22- CD]

Alicia was eventually referred, though she portrayed considerable frustration at the delay caused by her GP, especially as she had explained her family history of IBD to her GP.

A lack of GP knowledge when interpreting symptoms was described by participants. For Derrick, his GP admitted that he was unsure of what was causing his symptoms:

> *Around the age of 8 or 9, I was losing blood in the stools and I was told, although I remember the discussions with the GP, he didn't understand what was happening. If I obviously weren't so young he'd have said I had liver disease. But he discounted that because I was too young and I was anaemic as well so they started giving me vitamin B12 injections so I was having those at school regularly … Its more that the doctor couldn't work out what was happening. So he didn't see it so, I remember the conversations, well some of them, I remember the conversation emphasis was 'I don't know what's happening' … I must admit, my mother did say that moving house saved my life. That's what she said, changing GP* *[Derrick, 62- CD]*

One participant believed financial incentives were associated with her GP's reluctance to refer her to a specialist:

> *EC- Do you think they acted as a barrier to your delay in diagnosis?*
>
> *Lauren- The GP did, definitely, I did an OU in Health & Social Care and the gatekeeper to the NHS, the GP, yes, categorically, without a doubt. I was under NHS Scotland then and at the time, I don't know if it's still practice, NHS Scotland used to give them GP practice bonuses for not referring, so they used to get bonuses for not referring and I 100% believe that to be a factor as well.* *[Lauren, 45- CD]*

Further to delays in referral, there was evidence of GPs referring participants to incorrect departments in secondary care:

Alicia- I got the referral for gastro but I'd been first to other places like colorectal surgeons and everything, so once we got to gastro that was it then.

EC- How many times were you referred to the hospital before you went to gastro and they sorted you out?

Alicia- I think it was about three times … Yeah I saw two colorectal surgeons and then I think I saw, what's the one that deals with hormones and things Gynaecologist [sic endocrinologist]*, yeah I saw one of them as well to do with my periods.*

[Alicia, 22- CD]

Simon began to suffer with soreness in his back as well as his gastrointestinal symptoms, and was referred to a specialist. This specialist then referred him to the gastroenterology department:

I can remember going to see my GP around about the turn of the year, that year, 2000, and I think because I was going on about this soreness in the back, he referred me to a back specialist, or neuro specialist, I think he was trying to get rid of me actually, I think he thought, oh, I don't know what to do with you, you keep coming back and forth with this, maybe there's something going on, you know, so he referred me sideways to this gastro.

[Simon, 65- CD]

There was evidence of patients struggling to access their GP due to the nature of their symptoms. One participant recalled how her GP would not visit her at home due to her symptoms, which were perceived to be infectious. In the end, she became very unwell and was seen by an Out of Hours GP who admitted her to hospital:

But within those few days I then, I threw up the once. I had a telephone conversation with my GP at the time and they basically refused to see me and they refused me to go and see them and they refused to come and give me a home visit. So at the time I said you know 'I am really not well' and I'd started to have blood in my urine now because every time I drink it's coming out the other end [yeah]. So they were like 'Well you need to drink more', so I was like okay well you know, I work in the profession, I'm not silly but I didn't want to tell them that. So at the time I thought 'Well okay, just keep going, maybe I'm just being silly'.

[Joanne, 34- UC]

What is particularly noteworthy about Joanne is that her career in community healthcare suggests she likely has good health literacy. However, she did not seem to challenge her GP's management plan despite working in healthcare and believing that her symptoms were serious.

The reliance of the GP on blood tests to confirm or refute the presence of any illness was at the root of one participant's frustration, as he suggested that his GP was not very proactive in investigating his symptoms. Darren had symptoms of fatigue, abdominal pain, growth failure and diarrhoea. As a result of his GP's reluctance to refer him to a specialist, Darren's family decided to pay privately for a specialist appointment:

EC- I know you mentioned before that, you know, you were pushing to get this referral and at one point it did seem like your GP was going to refer you but then obviously you ended up going private. What happened with your GP there then?

Darren- Well…if I remember correctly…they did the blood tests and I had a blood test and another blood test and another blood test, and that was seemingly their only method of confirming or denying anything. And…they basically said at some point we may have to refer you if, you know, if something comes up on the blood test. So it was a bit of a, they started

mentioning it but then there was never really any 'yeah, we'll give you a referral'. And the blood tests, I don't know why the blood tests didn't seem to show anything

[Darren, 25- CD]

Simon, who was discussed previously when he described his fear of hospitals as contributing to his delayed diagnosis, reported that he wished his GP had encouraged him to have further investigations to identify a cause for his symptoms, in spite of his own reluctance. Simon suggests that his GP did not properly communicate the importance of these investigations, leading him to decline these tests for many years before being diagnosed:

They should have been more proactive, I think they should have put it to me a bit clearer and not allow me to kind of dodge the bullet, I think the patient, you know, if the patient turns up with certain symptoms, you know, they're ongoing and they're not clearing and you know…they really need to have some exploration to see what's going on, you shouldn't let the patient dictate the treatment, you know, you should say to the patient, you should try and find a way to understand that patient, to understand…what is it they're worried about… you really need to use a bit of psychology to get them to understand the need to go for these tests and I think that was a mistake on their part and I'll hold my hands up cause I didn't help. So you know, I could have had treatment a lot earlier, probably got an earlier diagnosis, I don't know, you know … I think nowadays, I think I have a feeling they would probably be a bit more, certainly forceful in their approach to me than it was then"

[Simon, 65- CD]

Lost or incorrect medical records and results was another factor for primary care delays as outlined by some participants:

I was lied to as well, things like they did a test like a calprotectin test to see what my inflammation levels were like and I'd ring up and they'd say 'oh yeah they're fine, yeah, no worries', and I went and when the hospital later looked back at them they realised that they were actually off the scale and then they were just telling me that there was nothing wrong with me … *[Alicia, 22- CD]*

Being unable to access test results was a considerable issue faced by one individual, particularly as she had to ask for the test to be done in the first place:

As soon as I went a few years later, when I was 17, and I said, 'I've got a sister with Crohn's. I want you to do a calprotectin,' because my mum said, 'You're just going to have to go in and ask for what you want'. They did do a calprotectin. I never heard back and I was told, 'If you don't hear back, everything is fine.' Six months later, I lost loads of blood. My mum said, 'That's absolutely definitely not fine. That's not normal.' I rung up and I said, 'What were my calprotectin results six months ago?' They refused to give it me. I still haven't had that and I've been told now that it's been lost. *[Emily, 20- CD]*

Emma reported that approximately 6 months after this incident she returned to her GP and another faecal calprotectin test was ordered. Her results showed significant inflammation and as her symptoms had not changed during this time, she believes the first calprotectin level was also abnormal. She was therefore of the view that had she received the results from this first test, she possibly would have been referred and diagnosed with CD.

Finally, prolonged and ineffective management for what was thought to be IBS was identified as a contributing factor to diagnostic delay. Participants felt that when the management for IBS was

ineffective at relieving their symptoms, their GPs should have investigated further or tried different medication:

> *Well it just seemed to be forever pepperminty things you know drinks and tablets and… I don't recall anything else coming to light, no … I think with them knowing my sister had got it* [CD]*, I think they probably seriously suspected that from an early stage but still kept treating it as IBS which was a bit frustrating, but I guess I mean I think that's what you hear with most people with Crohn's that we tend to have to go down the IBS route first*
>
> *[Pamela, 45- CD]*

Participants felt worried when they believed their symptoms were not being considered seriously by their GP:

> *I think maybe as well I was a bit afraid of what it could be, but I think I was a bit frustrated because I knew that there was more to it than what they were telling me to begin with and then the more you feel like you're not being listened to, I think you can blow things out of proportion and then I started to worry it was something really serious as well*
>
> *[Jess, 38- CD]*

Worsening symptoms, due to inactivity from participants' GPs, finally led them to establish their diagnosis. John had persisting symptoms over a long period of time, though he recalled that it was only when he rapidly lost weight that his symptoms were taken seriously:

> *John- I was having some weight loss, some unpleasant symptoms, yeah a massively increased bowel habit and maybe that was a factor, it wasn't really until things started speeding up that, you know the symptoms were dramatically worsening, that things began to change*
>
> *EC- Yeah, you felt like you were dealt with more urgently then?*

John- Yes, yes, I think that they thought 'right the weight, almost a stone a week I was losing' then suddenly it was like let's get you into hospital *[John, 56, CD]*

Moreover, issues were raised about delays in commencing IBD management as well as delays to diagnosis. Helen's consultant wrote to her GP asking to prescribe her Asacol (mesalazine) for her UC, however her GP did not do this, and suggested that it was Helen's responsibility to request the medication despite her being unaware about a prescription in the first instance:

I had mild, left-sided ulcerative colitis and I just found that out by ringing the doctors to ask if they'd had a report from the consultant and it came back 'yes you've got UC and they're going to send for you again in about 3 months'. I didn't have any treatment all the doctor was giving me during the summer was Buscopan. When I had my appointment to go back to see the consultant which by then was early the following year, he said 'how are you getting on with your Asacol?' and I said 'whats Asacol?' and he said 'it's what I told your GP to give you when we diagnosed your colitis'. I said 'well I've not had any'; so he was a bit cross about that and told me to go back to the doctor and find out why I hadn't been given it and it was just that because I was well, I wasn't moaning or nagging they just didn't prescribe it

[Helen, 53- UC]

Whilst most participants reported a lack of knowledge from their GP, Joanne reported a very different experience, recounting a consultation with an out of hours doctor who promptly identified the possibility of UC:

So I went to the out of hours doctor and it was just because by chance I think that this doctor, she agreed for us to go in to see her, she took one look, she said 'You're so dehydrated' … She looked through my medical history and she was like, she took time, I think that was the

difference. She knew I was unwell, she did my observations, they weren't obviously good because I wasn't very well. But she took time to read about my past medical history, she's an out of hour's doctor, but she's a fresh pair of eyes and then that's when she said 'Has anyone ever told you, you could have colitis?' *[Joanne, 34- UC]*

5.3.3 Sub-theme: systemic factors for delay

This sub-theme describes the organisational and administrative factors that contributed to delays in diagnosis as outlined by participants. These include long waiting times for specialist appointments and cancelled procedures. IBD was included as a differential diagnosis in one participant's case, though this was not identified by his GP practice. This previous diagnosis of IBD was only noticed when the participant read through his GP medical records, after he had been diagnosed with CD. He also describes reading comments left by his GPs that *"labelled"* him with mental health problems:

Brian- My son went through my notes with me and you can see this path before I went in- 'we don't know what other tests to do' and there again in big capitals- 'CROHNS' with three question marks then it actually said, 'been to the doctors again' … In my medical records it says 'this patient takes up too much time'

EC- How did you feel when you were reading that back?

Brian- Appalled, upset, because I thought this has gone on for so long. This is after I got diagnosed going through my GP records and they'd been so nice to me, I just look at is at yeah, labelled, he's got mental health issues *[Brian, 57- CD]*

Brian was upset to realise that a diagnosis of IBD had been considered by specialists but pursued no further, particularly as his GP implied he wasted their appointment time.

There is evidence that long waiting times to outpatient hospital appointments also contributed to diagnostic delays, as with Emily who was told she would wait 6 months to see a consultant:

> *They'd told me that they were going to refer me to the hospital and that I would probably end up needing a colonoscopy to do further investigations but before I'd have a colonoscopy, I'd have to see a consultant. This was in December and I was told that the wait time would be at least six months to see a consultant. We then paid privately for me to see a consultant two weeks later, purely because we knew how ill my sister* [who also has CD] *got in the six months that she was waiting to see someone* *[Emily, 20- CD]*

As previously discussed, Emily was not told the result of her first calprotectin level as, according to the GP practice, it had been lost. Therefore, she could have been waiting even longer to see the consultant if she had been diagnosed under the NHS. This was a problem that she reported her sister had also experienced before being diagnosed with CD.

Even though her GP was proactive in referring her, Charlotte recalled experiencing a long wait until the appointment:

> *I went to the GP like straight away, I managed to get an appointment quite quickly but the GP said to come back when I had the abdominal pain and just to keep an eye on the blood cause he didn't know whether it's just an infection … So I took that* [rehydration sachet] *away and tried that, I think 48 to 72 hours and I just still wasn't well at all, and the blood was getting more and more like every day, my mum took me back to the GP and then he said, we need to pursue it a bit further and investigate it and then sent me for an urgent referral, but even that took about five to six weeks take to be urgently referred across to the paediatric department* *[Charlotte, 28- CD and UC]*

Delayed colonoscopy was revealed as another systemic factor contributing to overall diagnostic delays. Despite being aware of a possible IBD diagnosis, Pamela's consultant did not wish to commence treatment before a colonoscopy confirmed the presence and extent of CD:

> *They put me through to the hospital for tests but obviously they take time and I think I had a barium meal quite quickly but the colonoscopy one was the one that just kept getting cancelled, it must have been cancelled quite a few times which then put off, because they kept saying 'well we want a baseline of your Crohn's' – I think they thought it was Crohn's, knowing it was in the family – but I think they wanted a baseline of my symptoms and how I was before they treated it but it kept getting cancelled and it got to the stage where I was so ill that they had to do something really, that's how I understood it anyway, that was my take on it.* *[Pamlea, 45- CD]*

A comparison between the management of older versus younger people was also raised by Emily. As there is an increased risk of colorectal cancer with older people, Emily agreed that they should be seen first, however she implied that her symptoms were taken less seriously due to her younger age, and subsequent lower risk of serious pathology:

> *For example, if I was an older person, I'd be more likely to have bowel cancer than a younger person but say, for example, the calprotectin result was raised because they had Crohn's, their diagnosis would have been completely the same as mine and quicker on the basis that it might have been more important but it might not have been. They've then got their Crohn's more under control because they're older which shouldn't really be the case.*
>
> *[Emily, 20- CD]*

5.4 Consequences of delay

This final theme encompasses the impact participants felt their diagnostic delay had had on their subsequent illness experiences and disease course. For instance, many participants turned to private healthcare for advice because of delays in NHS healthcare. Additionally, the impact of delays in diagnosis as experienced and cited by participants is discussed. This includes the participants' perceptions of how their delay has affected their symptoms and management.

Seeking medical advice from the private healthcare sector was described by many participants, as they felt that they could not wait for GP referrals, NHS appointments or investigations. All participants had positive experiences with private healthcare and were diagnosed soon after, with many describing an accelerated diagnosis when compared with experiences of NHS care:

> *I think I was 16, just about to turn 17. I went for an appointment with like a private doctor at the Nuffield … and I was diagnosed there … And he pretty much saw me straight away and went, 'Yeah, you don't look like you've got IBS to me', just looking at me. He said how pale I looked and things like that. And then he did all the usual like feeling your stomach and that kind of thing and said I felt very tense and felt very tender. And then he sent me for a colonoscopy and it was only on the colonoscopy that the Crohn's actually showed up, and I was diagnosed at that point* *[Darren, 25 CD]*

Josie remembered feeling satisfied with her interaction with the private consultant during the appointment:

> *So when we saw the consultant we explained what was going on, all my symptoms throughout the years and he was like 'If you put all those symptoms together it sounds like ulcerative colitis', so he was like 'If you wouldn't mind we could have a look right now in the office'. So he did, he had a little look and straight away he was like 'Yeah, you're inflamed*

and it's all redness and you've definitely got it', like straight away within the ten minutes he was like 'Yeah, I can confirm a diagnosis of ulcerative colitis'. And that was quite good because he didn't waffle about and he didn't want to just stick with bloods, he actually had a look, got straight to the point … He was speaking to me as well as my mother, he wasn't just ignoring me he was actually paying attention and he said a little bit about what the disease was and he told us our options, what we could do to help me and everything. He got straight to the point and he didn't just like give me a diagnosis and say goodbye or anything, he sat with us and explained a little bit and told me what I could do.

[Josie, 18- UC]

Josie explained that, by paying privately, she had a longer appointment with the specialist and was positive about having received a thorough explanation for her symptoms, as well as a discussion about the management plan; implying that this consultant spent more time talking to her than previous doctors.

The decision to seek private healthcare advice was influenced by financial factors. Some people utilised private healthcare insurance provided by their employer:

When I finally got to see a consultant after I got diagnosed and the results came through they couldn't find any appointments on the NHS over summer for 3 months and then I remembered I had private health insurance so 2 days later saw a consultant

[Sandra, 65- CD]

There was evidence that this uncertainty of the diagnosis despite worsening symptoms negatively impacted on participants' family members as well as participants. Alicia reported that her mother became increasingly worried, particularly as her GP displayed a lack of concern:

When you feel ill every single day it's really draining and when someone is not listening to you and just keep sending you away it's really very frustrating, I think my mom was just getting more and more worried because I'd just lose more weight, you look worse, you are anaemic, it wasn't good, it wasn't a good time *[Alicia, 22- CD]*

When asked about the impact of the delayed diagnosis on their IBD, participants had very different responses. Some participants provided evidence that a delayed diagnosis may have led to their IBD being more difficult to manage. Darren questioned whether he would have developed his stricture or adhesions, which resulted in him undergoing surgery, if he had been diagnosed quicker:

EC- Do you think that having a delayed diagnosis has impacted on your Crohn's at all?

Darren- Maybe because I wonder if maybe I wouldn't have gotten a stricture and because when I had my stricture removed, when I had my operation, they said there was an awful lot of adhesions. And I know often they're caused by other operations but I never had another operation and they said can be caused by Crohn's symptoms, which I didn't know. And so, and it was mentioned to me that it could have been because I'd had Crohn's symptoms for such a long time. So, and that definitely does have an impact on my intestines and stomach and things, definitely did have, and I wonder if I may not have had a stricture if I'd gotten all the right medication earlier *[Darren, 25- CD]*

Additionally, Emily reported that she believes that the long-term management of her CD may have been more effective if she had been diagnosed when her first faecal calprotectin was raised:

If it had been found by the GP, at that point, that my calprotectin was raised, I would then have paid to go privately to move things along because of what happened with my sister. If I could have then got that diagnosis within a month, I might not have had to get to that point.

It took me over a year of being on Infliximab to actually not having any symptoms anymore. I had to try numerous other medications before that. It took over 18 months to actually get to the point where I hadn't got any symptoms anymore … A delayed diagnosis has an impact because it's more severe and so I've found that it's harder to treat. Because it's more severe

[Emily, 20- CD]

Lauren also questioned whether she would have needed to undergo surgery if her diagnosis was not delayed:

EC- How has your delayed diagnosis affected you in terms of your Crohn's?

Lauren- I think if I'd have been treated earlier I may have avoided surgery for longer, if at all, perhaps, I can't guarantee that but that does cross my mind, you know it might not have become fibrotic, well it probably would have but it might have been delayed, I wouldn't have suffered the side effects of the weight loss, which then obviously, that has a massive impact on your life, and now I have a sort of bubbling resentment for the delay in diagnosis.

[Lauren, 45- CD]

However, there was variation observed in the data, as some participants believed that their diagnostic delay did not impact on the management of their condition. Pamela largely associates her symptoms with the relapsing-remitting nature of CD as opposed to her delayed diagnosis:

I think in the long term the delayed diagnosis hasn't had [an impact]*, because I did get back on my feet and obviously since then you know it's been the path of another chronic disease, you know, I've had periods when I'm fine and periods where I'm really not fine and I don't*

think that would be any different if I'd been diagnosed quicker I think that's just the nature of the disease *[Pamela, 45- CD]*

Although Josie did not believe her diagnostic delay influenced the medical management of her IBD, she acknowledged that an earlier diagnosis may have improved her mental wellbeing as it might have *"put* [her] *mind at peace"* to know the cause of her symptoms:

EC- So do you think your symptoms or the management of your condition would've been different if you were diagnosed earlier?

Josie- I don't know because it's like I had symptoms and if I'd got diagnosed before I got to the bleeding stage and the actually like damage being done, I don't know if they could've done anything until that point. So really I wasn't having inflammation markers and if I wasn't fully inflamed I don't think the medications would've been very good or even work. So even if I had a diagnosis I think it would've put my mind at peace and know I could do something about it if it does get worse, but I don't think we could've done anything in the early stages. *[Josie, 18- UC]*

One participant, who began experiencing symptoms as a teenager but was not diagnosed until adulthood, implied that had she been diagnosed as a teenager, this may have had more of a negative impact on her life. This opinion was not expressed by other participants:

EC- It sounds like you've been through so much sort of over the years though…

Lauren- In a way I'm kind of glad that I didn't, on reflection and you know going on social media which I never used to do, a lot of the young people, you see quite easily for some

people it becomes your life really young and I really think that if I had have known when I was young, it might have held me back *[Lauren, 45- CD]*

A consequence of one participant's delayed diagnosis is the negative opinion they have towards the NHS regarding IBD:

I've ended up suffering more but also delayed diagnosis has meant that I just thought, 'People don't really take Crohn's seriously.' Whenever I've spoken to someone and said, 'I'm not well enough to come today. I've got a bad Crohn's flare up,' I just think that people aren't going to take it as seriously because that was the general impression that the NHS has given me *[Emily, 20- CD]*

5.5 Qualitative results discussion

Sixteen participants took part in research interviews, varying by age and extent of diagnostic delay; with participants with CD generally citing longer delays than those with UC. Key factors they believed contributed to their delayed diagnosis included poor proactivity from their GPs and poor recognition of symptoms. Whilst some patients believed their delayed diagnosis had impacted upon their IBD, others believed similar outcomes would have occurred even if diagnosed sooner.

5.5.1 Misdiagnosis

Key misdiagnoses in both participants with UC and CD included IBS and gastroenteritis. A diagnosis of IBS seemed to be explained by the presence of stressors occurring in participants' lives at the time of symptoms, particularly workplace stress. Qualitative research into IBS has been carried out from both a clinician and patient perspective, by Dixon-Woods and Critchley (2000). Although these patients had a correct, confirmed diagnosis of IBS, they provide an interesting insight into the process of being diagnosed, some of which is applicable to this study. Of the fourteen patients with IBS, some were concerned about the significance of symptoms, similar to participants interviewed in the present study. Some of the people interviewed by Dixon-Woods and Critchley also described a feeling that their GP was not taking their IBS symptoms seriously and they rejected the notion that their symptoms were psychological in origin. This was a common finding amongst IBD participants who had being misdiagnosed with IBS, who reported repeatedly seeking help from their GPs to no avail. The twelve clinicians interviewed in Dixon-Woods and Critchley study, six GPs and six gastroenterologists, offered mixed opinions towards IBS. When diagnosing IBS, one GP highlighted the importance of excluding all other diagnoses. It is surprising that only one GP in their study acknowledged the importance of excluding other diagnoses; however this does appear to reflect the patients in the present study perceived the attitude of GPs, as participants recalled

being left on medication for IBS even when it was ineffective. Whilst a misdiagnosis of gastroenteritis was discussed by many participants, there appears to be an absence of literature in this field. A possible reason for this is the shorter disease duration of gastroenteritis, as when participants experienced persisting symptoms, IBS was then considered a more appropriate diagnosis.

An unexpected finding of this research was the misdiagnosis of IBD symptoms with mental health conditions. Whilst psychiatric conditions can cause physical symptoms, it appears more sensible to exclude a physical origin of symptoms before diagnosing a psychiatric condition. This was particularly poignant with the participant who felt that he had been 'labelled' with mental health problems and all of his symptoms were linked to this. Incorrectly attributing physical symptoms to psychological causes, known as diagnostic overshadowing, has been explored in literature. For instance, an interview study with emergency department clinicians in London about diagnostic overshadowing found that some clinicians may demonstrate ingrained attitudes to mental health patients and do not explore possible physical causes of symptoms (Shefer, Henderson, Howard, Murray, & Thornicroft, 2014). One psychiatric nurse in this study recalled being called to see a mental health patient who was deemed psychotic but in fact had fractured his foot and was in severe pain. Psychosis, which may include symptoms like hallucinations, delusions and changes to speech or behaviour can be caused by physical conditions, including sepsis, hypoglycaemia or low blood sugar, systemic lupus erythematosus and thyroid disease (Griswold, Del Regno, & Berger, 2015). This demonstrates a more general need for clinicians to consider and exclude the possibility of a physical condition before diagnosing a psychiatric issue.

5.5.2 Participant factors for delay

Participants acknowledged that they may have contributed to their delay in diagnosis. Where participants felt they did not personally contribute to their delayed diagnosis, they explained that concerns about their symptoms, having a family history of IBD and lack of embarrassment to discuss symptoms with medical professionals prompted them to consult sooner. Participants with a family history seemed to demonstrate better knowledge of IBD, with many questioning whether they had the condition before their diagnosis. Despite this prior understanding of IBD, they still experienced delays to diagnosis.

The participant-related factors for delay found in this study can be mapped onto Andersen's Model of Total Patient Delay (Andersen, Cacioppo, & Roberts, 1995). This model provides an overview of possible decision-making factors by patients that may cause them to delay seeking medical help, ranging from when they detect the symptoms to when they make an appointment to seek advice for these symptoms. These different areas of delay include 'Appraisal delay', where the individual associates their symptoms with an illness, which may differ from the condition they actually have; 'Illness delay' which is the time from the patient's perceived sign of illness to deciding to seek medical advice; and 'Behavioural delay', which is the time taken to act on the decision to see a medical professional by arranging an appointment (Andersen et al., 1995). This model was utilised to explain participant delays in the diagnosis of cancer in a systematic review by Walter et al. (2012), which found that the nature of symptoms and misattribution of symptoms to benign conditions, like IBS in bowel cancer, were common reasons for appraisal delays. Behavioural delays were associated with barriers to consulting such as holidays and other life events, as well as the time taken to come to terms with the possible cause behind the symptoms when cancer was suspected (Walter, Webster, Scott, & Emery, 2012). There are similarities between the findings of this systematic review and the qualitative research conducted in this thesis, in that misattribution of symptoms to other conditions was described, as participants believed their symptoms were

initially caused by gastroenteritis. However, behavioural delays were not found to be a pertinent issue for most participants in the present study, as they persistently sought healthcare advice even though their symptoms were not taken seriously by their GPs. Therefore, whilst no barriers were identified to consulting once participants had made the decision to seek help, these findings suggest that there is a need to reduce IBD patients' initial Appraisal delay. It may be that increasing awareness of IBD more generally, through health promotion campaigns, for example, could help to reduce this delay. Whilst patients can be reassured that GI symptoms are initially likely to be caused by an acute illness such as gastroenteritis, it is important for patients to recognise that if symptoms persist and are particularly severe this could indicate IBD and therefore they should not delay in making the decision to consult.

5.5.3 Healthcare factors for delay

Primary care factors for delay were common reported by participants, and similar factors have also been reported by participants in qualitative studies into other long-term conditions. In research exploring the delays in diagnosis of endometriosis, participants similarly recalled how their GPs had normalised their symptoms or performed general, non-discriminatory tests (Ballard, Lowton, & Wright, 2006). This led many to persistently present to their GPs with problems, as was also found amongst the participants in the present study. Participants in the present study also described delays even when asking their GP whether they could have IBD due to a positive family history. This was also mirrored in the delayed diagnosis of endometriosis where the participants' mothers had endometriosis (Ballard et al., 2006). This may suggest that there is a need for GPs to be more informed about conditions where there are possible genetic causes, such in the case of IBD, and as a result to pay more attention to the patients' family history, particularly when this is flagged up by the patients themselves.

Key systemic factors that participants felt led to a delay in their diagnosis were missing medical records, miscommunication of information within medical records and delayed colonoscopy appointments. With the large volume of patients using the NHS, errors in communication and medical notes may occur. However, a mixed-methods study by Burnett, Deechland, Franklin, Moorthy and Vincent (2011) found that key clinical information, particularly diagnostic or radiologic test results, was omitted from patient records in 15% of outpatient consultations across three teaching hospitals in the UK, from a total of 1161 patients. According to fifteen members of staff involved in transporting, using or writing in clinical notes who were interviewed, missing information led to the cancellation of operations in fifty-five patients and put thirty-five patients at risk of harm. Factors associated with missing medical data included complex medical problems whereby patients are under the care of many specialists, merging hospitals and temporary staff (Burnett, Deelchand, Franklin, Moorthy, & Vincent, 2011). This study, amongst others, demonstrates that incomplete clinical records is an important issue and can impact patient healthcare, as evidenced from the participant accounts within this thesis. Similarly, a review investigating the delays in diagnosis of lung cancer found that poor co-ordination across medical services and inaccessibility of diagnostic procedures and results contributed to delay (Malalasekera et al., 2018). Whilst the interview findings suggest that systemic failures contribute to delays in IBD diagnosis, existing research in this field highlights the significance of this issue across the healthcare service.

5.5.4 Consequences of delay

Conflicting opinions from participants arose about whether the delays in diagnosis impacted on their IBD in the longer term. Some participants believe they struggled to reach remission or required surgical intervention because of their delay. However, others accepted that the course of their IBD is part of having a chronic, relapsing-remitting condition, and therefore did not make a

link between delay and disease severity. As described in Chapter 1 section 1.2, there is evidence that a delay in diagnosis contributes to complications of the disease. For instance, in a study conducted by Szanto, et al. (2018) the rates of surgery and use of biological therapy were significantly increased in CD and UC patients who had been diagnosed over one year after symptom onset (p=0.012 and p=0.002 respectively). A more complicated disease course was found in a study by Li *et al*., where the rate of subsequent surgery was 84.7% in those with a diagnostic delay of over thirty-four months and 62.4% in delays below 34 months, although stenosis, fistulae and perianal surgery were not significantly different between the two groups. In a cross-sectional study by Pellino, Sciaudone, Selvaggi and Riegler (2015), a diagnostic delay of over eighteen months was associated with an increased risk of needing a stoma (P=0.003) and developing surgical complications more frequently (P=0.03). It is also important to acknowledge the participants' impact of delay from their own perspectives. Many expressed negative emotions and feelings towards their delayed diagnosis which could have an adverse effect on the therapeutic relationship between the participant and healthcare professionals involved in their care. In qualitative research undertaken in a teaching hospital in Canada, participants who were recruited from various clinical sites around the hospital shared their insights regarding the need for physicians should listen to patients in order to improve the physician-patient relationship. They described how feeling that their physician listened to them led to patients taking greater ownership of their health as they felt the physician respected their opinions, as opposed to feeling "ridiculed" and angry (Jagosh, Donald Boudreau, Steinert, Macdonald, & Ingram, 2011). Findings in the present qualitative study mirrored some of findings in the study by Jagosh *et al*., as participants reported valuing the time the consultant spent with them during their private consultations, in contrast to feelings of resentment when their concerns about symptoms were incompletely addressed by GPs. However, whether negative experiences with healthcare professionals has impacted on IBD management or relationships with clinicians was not explored by participants in the study included within this thesis.

Five participants that were interviewed described some involvement of private healthcare in gaining a diagnosis, particularly in light of long NHS waiting times and also the unresponsiveness of their GP to refer them. Such findings are reflected in a recent interview study conducted with participants who have received a cancer diagnosis, with most patients finding that consulting the private sector aided their diagnosis (Parsonage, Hiscock, Law, & Neal, 2017) . As described by Doyle and Bull, individuals acknowledge that their medical needs are in competition with the medical needs of numerous others within the NHS, so private healthcare can be a useful alternative for them to access medical care (Doyle & Bull, 2000). In the present study, it appeared that for some participants, private healthcare was deemed the only way for participants to seek answers for their symptoms, which has an associated cost burden for the patient. The positive experiences of private healthcare as described by participants and the lack of progress they were making under the NHS demonstrates a need for the NHS to improve the care towards individuals with IBD in order to reduce diagnostic delays. This is particularly significant with IBD in younger people, as older people may receive their diagnosis of IBD by being referred under the NHS two-week wait referral system which is used to diagnose cancer. The absence of referral system for younger people with suspected IBD means they often wait longer to see an NHS consultant, in the meantime their symptoms may worsen and they may become unwell.

5.5.5 Strengths and limitations

Adopting a semi-structured approach to interviewing as described in Chapter 5 was advantageous as it allowed me to explore aspects of participants' delay which were deemed important to them, but which I had not originally considered. In this sense, facilitating conversation led by the participant provided much richer data. I also felt that the topic guide provided a comprehensive overview to explore participant experiences whilst allowing the flexibility to explore different topics as guided by the participant.

To ensure trustworthiness of the transcripts returned from the transcription company, the content was checked against the audio-recording to ensure accuracy of the data before analysis. Data analysis is dependent upon the accuracy of the data, therefore checking the transcripts ensured high quality analysis. The transparency of the data analysis offers another strength of this research, as the method of thematic analysis has been outlined in the thesis along with evidence of this process, such as the thematic maps **(Appendix 11)**. The detail of reflexivity ensures identification of how my background as a medical student may have influenced this process, demonstrating rigor towards the analysis stage as it allows the reader insight into how I interpreted the data.

Using thematic analysis was useful, particularly when exploring misdiagnoses or participant factors for delay as it allowed me to explore into the data set as a whole, whilst not losing sight of the individuality of each participants' experiences. This allowed me to make comparisons and contrasts between the experiences of different participants and identify possible trends regarding key factors that contributed to, or resulted from, the diagnostic delay.

The original intention was to conduct the qualitative research using findings from the systematic review, as the values for the extent of diagnostic delay extracted from the studies included in the systematic review would have been used to establish the criteria for inclusion in the interviews. However, the scale of the systematic review meant that both research approaches were undertaken simultaneously. Therefore, a minimum delay of three months was influenced from the findings from Cantoro *et al*. (2017), following discussion with supervisors as opposed to being influenced by the review findings, which may have been a misrepresentation of diagnostic delay as the systematic review findings demonstrated median delays ranging from two months to one or two years depending on the diagnosis. This meant participants with delays between 2-3 months were not included in the qualitative study; therefore, the qualitative sample may be less representative of delay presented within the systematic review studies.

In addition, the use of convenience sampling risks a poor spread of participant characteristics, including age, gender and IBD phenotype as there is no means of controlling their characteristics. This is apparent from the larger proportion of participants with CD who were interviewed, though from the findings of the systematic review, diagnostic delay of CD is more problematic that delays in UC diagnosis therefore exploring diagnostic delay of CD within these interviews was beneficial. However, the participants interviewed demonstrated variation in age, length of diagnostic delay and occupation (**Table 5.1.1**). It is worth highlighting that whilst patients with a range of diagnostic delay were recruited, convenience sampling may have led to the inclusion of participants with more protracted diagnostic delays, as they may have dissatisfaction at their diagnostic journey and want to involve themselves in research. In spite of this, the focus of the qualitative research was to establish reasons for and consequences of diagnostic delay as opposed to providing the extent of delay.

Similarly, the recruitment methods used may have led to the exclusion of certain groups from partaking in the study, as they may not use social media. There has always been an assumption that older people may not use social media and a systematic review assessing the use of social media for recruiting research participants found an over-representation of participants of white ethnicity as well as young adults and those with a higher degree of education (Whitaker, Stevelink, & Fear, 2017). Unfortunately, details of ethnicity, geographical location or education were not obtained from participants interviewed in the research within this thesis. However, from my experience of social media recruitment, it was not a barrier to recruiting people of older ages (i.e. over 60 years old), and recruiting from the C&CUK meeting that that it was also possible to invite eligible individuals who I may not have been able to access through social media.

A final shortcoming of this qualitative research is the absence of a second coder. The role of this second coder is to analyse the transcripts themselves and to discuss their interpretations of the data with the first coder, which deepens the understanding of the data by offering a different

perspective (Berends & Johnston, 2005). Due to the absence of a second reviewer, it was not possible to obtain different insights and interpretations of data.

5.5.6 ***Chapter summary***

This chapter outlines the findings from the interviews conducted with the sixteen participants recruited. The following chapter provides an overall discussion of the thesis, where the results from the systematic review are compared with the qualitative findings, which is typical of the convergent mixed method design used within the thesis.

6 Discussion

This final chapter reflects on the issue of diagnostic delay in Inflammatory Bowel Disease (IBD) with regard to the systematic review and qualitative study, as well as reflecting on the research process and exploring the implications of this research on future research and clinical practice.

6.1 Summary of findings

The aim of this research was to establish the extent of diagnostic delay of IBD together with possible reasons why it occurs and subsequent impacts that this delayed diagnosis may have on both the disease course and the patient. This was achieved by undertaking a systematic review of published literature which reported the extent to which IBD diagnosis can be delayed and by conducting semi-structured interviews with individuals who have experienced a delay in diagnosis of IBD.

The findings of the systematic review demonstrate that diagnostic delay of IBD has, and continues to, impact negatively on patients. Whilst there has been little improvement reducing the time delay in receiving a diagnosis of Crohn's Disease (CD) over time, it would appear that diagnosis of Ulcerative Colitis (UC) is becoming more prompt. The extent of delayed diagnosis of IBD is unrelated to geographical region, but greatest delays in receiving a diagnosis of CD occur due to factors within the healthcare systems as opposed to patients' failure to present.

Diagnostic delay upon entering the healthcare system may be related to key misdiagnoses described by participants in their interviews, such as Irritable Bowel Syndrome (IBS), mental health issues and haemorrhoids. Participants cited systemic failures, incorrect interpretation of symptoms and poor proactivity of GPs as common healthcare factors for delay. Issues surrounding perceived

insignificance of symptoms, embarrassment and fear were perceived to contribute to participant to delay.

6.2 Diagnostic delay at a population and individual level

Combining the findings from the systematic review and qualitative research, as part of a convergent mixed method design, demonstrates the issue of a delayed diagnosis of IBD. They both highlight how diagnostic delay has been an issue over time, as the systematic review papers were published between 1971 and 2019 and some participants that were interviewed received their diagnosis between two and fifty-two years ago. In the systematic review, the diagnostic delay of CD was generally longer than the delay in UC diagnosis. This was mirrored in the qualitative research, as the median reported delay for UC diagnosis was 2 years and was 8 years for CD. A possible explanation of this could be the complex and varied presentation of CD, particularly as it can affect any part of the GI tract and so a variety of symptoms may occur meaning there can be many differential diagnoses (Aghazadeh et al., 2004). In contrast, UC often presents with rectal bleeding, an alarming symptom which may cause individuals to seek medical advice more quickly (Novacek et al., 2019)

There are similarities in the findings of both research approaches. For instance, data on consultation and healthcare delays was present in six articles sourced in the review. The general conclusion from these was that though delay did occur due to actions of patients, the majority of delays occurred when the patient entered the healthcare system and could be linked to the attitude or decisions of the healthcare professional, commonly a GP. This was explored in the interviews, with participants providing a variety of opinions on how they influenced their delay. Some participants felt that their symptoms were only minor and thus did not need to see their GP. Others described trying to manage with their symptoms until they worsened. Worry and fear of the

underlying cause also dissuaded some participants from seeking help sooner. For participants who did not have a family history of IBD, they were largely unaware of the condition. In other medical conditions, patient education of certain disease has been improved with campaigns to raise awareness. Examples include the Headsmart campaign, which informs people of the symptoms of brain cancer in children through the distribution of patient information leaflets; and the act FAST campaign for identifying strokes which has been a national advertisement campaign on televisions and posters (Headsmart, The Brain Tumour Charity; Stroke.org). Many participants felt that their GP contributed to their delayed diagnosis through failing to arrange tests and referrals- even when participants were repeatedly presenting to them with their concerns. Other delays were caused by long waiting lists for appointments and cancelled procedures. Action has been taken to improve healthcare professionals' awareness of medical conditions. For instance Crohn's and Colits UK (C&CUK) have been working with the Royal College of General Practitioners on a project called IBD spotlight, in order to improve primary care diagnosis and support people with IBD by providing clinicians with information to determine whether a patient has IBD or not. Headsmart also provides information for clinicians for when to reassure or refer a child with worrying symptoms.

One paper included in the systematic review explored the possible effect of a diagnosis of IBS on the delay in diagnosis of IBD. This study by Burgmann *et al*. (2006) found that a diagnosis of IBS, either a real diagnosis preceding IBD or a misdiagnosis, was linked to longer IBD delays. Misdiagnoses of IBS was a pertinent finding from interviews with eight participants. In addition, this misdiagnosis was cited as a healthcare factor for delay when participants felt that they were not further investigated despite the management for IBS being ineffective.

6.3 Clinical implications

A central finding from this body of research, from both the systematic review and qualitative research, is that there are significant diagnostic delays in IBD. For instance, a number of participants from the interviews were diagnosed with IBS for a long period of time before eventually being diagnosed with IBD. These delays likely occur at the level of primary care and care needs to be afforded to educating GPs around IBD but particularly around screening tests such as faecal calprotectin. Many participants described persistently asking their GP for a referral to secondary care services which did not happen, therefore GPs should be quicker to refer patients whose symptoms are challenging to manage as this could indicate an incorrect diagnosis. Moreover, GPs should also obtain a family history of medical conditions and, when a family history of IBD is present, seriously consider this diagnosis in patients presenting with chronic symptoms suggestive of IBD. As described above, many campaigns to raise awareness of conditions have been successful, and as this research highlights the issue of diagnostic delay in IBD, similar strategies could be used to improve awareness of IBD amongst healthcare professionals and the general public.

The main issues surrounding secondary care delays were largely the long waiting times for appointments. This is surprising considering that NICE guidelines state that all patients with suspected IBD should have an appointment with a specialist within four weeks (NICE 2015). This timeframe has been reiterated by the 2019 IBD Standards, although patients should be seen sooner if clinically necessary. The 2019 IBD Standards are a list of items that represent high quality IBD care, including pre-diagnosis, flare management, surgical and inpatient care, which has been devised by healthcare professionals. In addition to the four week referral timeframe, they state that patients should be informed about diagnostic pathways and the timescale by which investigations will be completed (Kapasi et al., 2019). However, in the qualitative research many participants described waiting up to six months for an appointment, which highlights failures in the

NHS to comply with this guidance and failures in primary care where GPs did not seem to recognise that symptoms could possibly be caused by IBD. As such, increased awareness of the four week referral pathway is needed, as well as increased capacity within outpatient appointments so that more patients can be seen. In practice, increasing capacity with the same number of gastroenterologists is challenging, particularly as they diagnose and manage a range of different conditions. There has been minimal research recently conducted into improving referral systems for gastroenterological pathology. In a previous study has been conducted by Jiwa *et al*. in which an electronic pro forma was piloted and educational sessions were provided by a colorectal surgeon to guide primary care as to which patients required urgent referral, which proved unsuccessful and it threatened the established practice and protocols in primary care (Jiwa et al., 2006). This study demonstrates that adapting referral guidelines can be challenging to implement, however it may improve patient times to diagnosis and therefore further research efforts should be made to refine referrals for urgent GI pathology. IBD Standards acknowledges that certain NHS services may not meet their statements, though argue that improvements to service quality can be made as a result of implementing the Standards and consequently enhance patient care (Kapasi et al., 2019). However, applying the suggestions in the 2019 IBD Standards to clinical would improve diagnostic delays in patients with suspected IBD.

The diagnosis of IBD was particularly problematic in both younger participants from the interviews, where delays ranged from 2 years to 26 years in participants aged under 16 years old at symptom onset. As paediatric patients were excluded from the systematic review, no comment can be made comparing age and diagnostic delay within the systematic reviews, though older people experienced prolonged diagnostic delays than their younger adult counterparts. There is literature which suggests that the diagnosis of paediatric IBD is more challenging at a younger age, leading to longer delays (Nambu, Hagiwara, Kubota, & Kagimoto, 2016; Sawczenko & Sandhu, 2003; Timmer et al., 2011). Consequently, clinicians should consider a diagnosis of IBD in adolescents and the elderly. As described above, the minimum wait of four weeks for individuals may have reduced

diagnostic delays for some of these participants so improving awareness of this referral guidance should be increased. This would benefit the younger population in particular, as older patients with GI symptoms are more likely to be referred under the two week wait rule (K. Patel, Doulias, Hoad, Lee, & Alberts, 2016). Previous research has identified that the peak onset of CD is between 20 to 30 years old, and 30 to 40 years old for UC (Cosnes, Gower-Rousseau, Seksik, & Cortot, 2011), so a referral pathway for IBD is highly likely to benefit this age group, who do not fulfil the criteria for referral under the two week wait rule.

6.4 Avenues for further research

The systematic review conducted in this thesis demonstrates that diagnostic delay of IBD is an important issue amongst adults, however this has not been explored in the paediatric population as these papers were excluded from the review. An important next step from this research is to conduct a systematic review exploring diagnostic delays in paediatric IBD. Age may contribute to diagnostic delay, as evidenced by the findings of this systematic review, so comparing delays in paediatric IBD with age of symptom onset and diagnosis may provide insight into ages more at risk of diagnostic delay. In addition, late adolescent years (i.e. 16 to 18 years old) can be problematic in healthcare when patients fall between paediatric and adult services, so exploring the impact of age on diagnostic delay could be achieved by subgroup analyses based on age.

Further research into the impact of faecal calprotectin on diagnostic delay should be undertaken, as this investigation was not referred to in papers within the systematic review. This was because most of the research was conducted before the introduction of this investigation. Current research demonstrates that it is an effective tool to differentiate IBD from IBS, therefore it would be expected that an abnormal faecal calprotectin level would reduce delays (Banerjee et al., 2015). Undertaking research that identified a reduction in diagnostic delay following the use of faecal

calprotectin would strengthen the use of this test in clinical practice. This could be achieved by conducting a randomised control trial in which 'usual care', involving the absence of faecal calprotectin testing depending on familiarity and use of the test, is compared with strict implementation of the guidelines.

Further to the novel qualitative research included within this study, factors which may increase an individual's risk of a delay in diagnosis of IBD should be identified, as this can educate clinicians about certain factors to observe in patients which may indicate IBD. It would be beneficial to explore patient and healthcare factors for delay, as conducted in this thesis, in a larger population to look at sub-categories of reasons for delay. Reducing recall bias could be achieved by recruiting individuals at the point of diagnosis. Stratifying patients based on their IBD phenotype and the extent of diagnostic delay they experienced may identify different risk factors that contribute to varying degrees of delay. Purposive sampling to recruit participants from different ethnic backgrounds may identify additional risk factors that contribute to diagnostic delay and can ensure future reductions in time to diagnosis. The qualitative research within this thesis involved patient participants, so interviews with healthcare professionals such as GPs and gastroenterologists, for example, could be conducted to explore their perceptions of delays in IBD diagnosis. Combining these findings with the results from the patient interviews would provide a comprehensive overview of factors contributing to delay as well as possible consequences.

The findings of this systematic review provide information of the extent of diagnostic delay, however further studies analysing clinical outcomes based on diagnostic delay could be performed. Various studies have already completed similar research, but a larger cohort and longer follow-up could demonstrate links between delayed diagnosis and worse clinical outcomes.

6.5 Conclusions

Diagnostic delay of IBD is an important issue faced by individuals worldwide. The extent of delay is unacceptably protracted, with patients experiencing symptoms for many months or even (in the most serious incidents) years without investigation or explanation. Failure of healthcare professionals to recognise symptoms as well as poor patient education of IBD are likely contributing factors. There is a propensity for clinicians to attribute symptoms of IBD to more prevalent conditions such as IBS and gastroenteritis, delaying both the diagnosis and treatment of IBD. Consequently, some individuals may experience complications of the disease such as fibrosis and bowel obstruction, requiring strong immunosuppressive medication or surgical intervention. This could be reduced if the diagnosis is established promptly. As such, improving patient and healthcare knowledge of IBD is important, especially in the use of the faecal calprotectin test as a diagnostic tool in primary care. Reducing the interval between referral and specialist appointments would also be an important step.

6.6 Personal reflections

I was enthusiastic to complete an MPhil qualification in my intercalated year as I have learned much about medical research during previous academic years and I wanted the chance to conduct research of my own. My interest in gastroenterology has developed during my university studies, particularly in a complex disease like IBD where diagnosis and management can be challenging. Completing research in the diagnostic delay of IBD has been rewarding and I hope that further research into this important aspect of the IBD patients' disease course is undertaken. I particularly enjoyed the opportunity to conduct mixed methods research as the results from both the systematic review and qualitative research demonstrate that diagnostic delay in IBD is an issue, therefore I feel I have contributed to an under-investigated area of research.

Firstly, I will discuss my experiences of doing the systematic review. I have learned many new skills that will benefit my future career in clinical medicine, including devising a search strategy and appraising articles. My most challenging experience of completing this systematic review was managing the large volume of references and sourcing the full texts to articles, particularly as there were many conference abstracts. I found the review process most enjoyable, especially when I began to identify papers relevant to my research question. Collating the data to conduct the narrative synthesis was also a rewarding aspect of the process.

Regarding the qualitative research, I enjoyed collecting data through interviewing, as each participant provided valuable insights into their delayed diagnosis. I believe I have captured the key issues discussed and presented them appropriately within each theme. As a future healthcare professional, I found their accounts of primary and systemic factors for delay sometimes saddening to hear, particularly when they felt their GPs were not listening to them. I hope that research in this field is published to ensure improved identification of IBD by both healthcare professionals and the lay population. The main challenge I faced was applying thematic analysis to my data, as I had no experience of analysing qualitative data before. For example, I found it difficult to aggregate codes together to create a theme, as initially there was extensive overlap between themes. However, with further refinement, I devised the three distinct themes that are discussed in detail within Chapter 5.

This thesis has been a rewarding challenge and I sincerely hope that the subsequent publication of this work demonstrates to healthcare professionals and researchers alike that delays in IBD diagnosis are a significant problem, paving the way for future research that will reduce delays and uncertainty amongst individuals with IBD.

Reference List

A. Brierley, J. (2017). The role of a pragmatist paradigm when adopting mixed methods in behavioural accounting research. In International Journal of Behavioural Accounting and Finance (Vol. 6). https://doi.org/10.1504/IJBAF.2017.10007499

Abreu, M. T., & Harpaz, N. (2007). Diagnosis of colitis: making the initial diagnosis. Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association, 5(3), 295–301. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17368227

Adegbola, S. O., Pisani, A., Sahnan, K., Tozer, P., Ellul, P., & Warusavitarne, J. (2018). Medical and surgical management of perianal Crohn's disease. Annals of Gastroenterology, 31(2), 129–139. https://doi.org/10.20524/aog.2018.0236

Aghazadeh, R., Zali, M.-R., Bahari, A., Amin, K., & Ghahghaie, F. (2004). Inflammatory bowel disease in Iran: A review of 448 cases. Archives of Iranian Medicine, 7(3), 210–216. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=39468130

Ahnen, D. J., Wade, S. W., Jones, W. F., Sifri, R., Mendoza Silveiras, J., Greenamyer, J., … You, Y. N. (2014). The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clinic Proceedings, 89(2), 216–224. Retrieved from http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=145326&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=0025-6196&volume=89&issue=2&spage=216

Al Jassas, B., Khayat, M., Alzahrani, H., Asali, A., Alsohaimi, S., ALHarbi, H., … Mahbub, M. (2018). Gastroenteritis in adults. In International Journal Of Community Medicine And Public Health.

https://doi.org/10.18203/2394-6040.ijcmph20184250

Albert, J. G., Kotsch, J., Kostler, W., Behl, S., Kaltz, B., Bokemeyer, B., … J., H. (2008). Course of Crohn's disease prior to establishment of the diagnosis. Zeitschrift Fur Gastroenterologie, 46(2), 187–192. https://doi.org/https://dx.doi.org/10.1055/s-2007-963524

Almeida, F., Faria, D., & Queirós, A. (2017). Strengths and Limitations of Qualitative and Quantitative Research Methods. In European Journal of Education Studies (Vol. 3). https://doi.org/10.5281/zenodo.887089

Andersen, B. L., Cacioppo, J. T., & Roberts, D. C. (1995). Delay in seeking a cancer diagnosis: Delay stages and psychophysiological comparison processes. British Journal of Social Psychology, 34(1), 33–52. https://doi.org/10.1111/j.2044-8309.1995.tb01047.x

Autenrieth, D. M., & Baumgart, D. C. (2012). Toxic Megacolon. Inflammatory Bowel Diseases, 18(3), 584–591. Retrieved from http://dx.doi.org/10.1002/ibd.21847

Balla, J., Heneghan, C., Goyder, C., & Thompson, M. (2012). Identifying early warning signs for diagnostic errors in primary care: a qualitative study. BMJ Open, 2(5), e001539. https://doi.org/10.1136/bmjopen-2012-001539

Ballard, K., Lowton, K., & Wright, J. (2006). What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. Fertility and Sterility, 86(5), 1296–1301. https://doi.org/10.1016/j.fertnstert.2006.04.054

Banerjee, A., Srinivas, M., Eyre, R., Ellis, R., Waugh, N., Bardhan, K. D., & Basumani, P. (2015). Faecal calprotectin for differentiating between irritable bowel syndrome and inflammatory bowel disease: a useful screen in daily gastroenterology practice. Frontline Gastroenterology, 6(1), 20 LP – 26. https://doi.org/10.1136/flgastro-2013-100429

Banerjee, R., Pal, P., Girish, B., & Reddy, D. N. (2018). Risk factors for diagnostic delay in Crohn's disease and their impact on long-term complications: how do they differ in a tuberculosis

endemic region?. Alimentary Pharmacology and Therapeutics, 47(10), 1367–1374. https://doi.org/http://dx.doi.org/10.1111/apt.14617

Basaranoglu, M., Sayilir, A., Demirbag, A. E., Mathew, S., Ala, A., Senturk, H., … A., A. (2015). Seasonal clustering in inflammatory bowel disease: A single centre experience. Expert Review of Gastroenterology and Hepatology, 9(6), 877–881. https://doi.org/http://dx.doi.org/10.1586/17474124.2015.1025054

Bassi, A., Dodd, S., Williamson, P., & Bodger, K. (2004). Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut, 53(10), 1471–1478. https://doi.org/10.1136/gut.2004.041616

Baumgart, D. C., & Carding, S. R. (2007). Inflammatory bowel disease: cause and immunobiology. Lancet (London, England), 369(9573), 1627–1640. https://doi.org/10.1016/S0140-6736(07)60750-8

Bernell, O., Lapidus, A., & Hellers, G. (2000). Risk factors for surgery and postoperative recurrence in Crohn's disease. Annals of Surgery, 231(1), 38–45. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10636100

Bernstein, C. N. (2015). Treatment of IBD: Where We Are and Where We Are Going. American Journal of Gastroenterology, 110(1). Retrieved from https://journals.lww.com/ajg/Fulltext/2015/01000/Treatment_of_IBD__Where_We_Are_and_Where_We_Are.16.aspx

Bochner, B. S. (2000). Road signs guiding leukocytes along the inflammation superhighway. Journal of Allergy and Clinical Immunology, 106(5), 817–828. https://doi.org/https://doi.org/10.1067/mai.2000.110813

Boyatzis RE (1998) Transforming Qualitative Information. Sage: Cleveland

Bramer, W. M., de Jonge, G. B., Rethlefsen, M. L., Mast, F., & Kleijnen, J. (2018). A systematic

approach to searching: an efficient and complete method to develop literature searches. Journal of the Medical Library Association : JMLA, 106(4), 531–541. https://doi.org/10.5195/jmla.2018.283

Braun, V., & Clarke, V. (2006). Using Thematic Analysis in Psychology. In Qualitative research in psychology (Vol. 3). https://doi.org/10.1191/1478088706qp063oa

Burgmann, T., Clara, I., Graff, L., Walker, J., Lix, L., Rawsthorne, P., … Bernstein, C. N. (2006). The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis--how much is irritable bowel syndrome?. Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association, 4(5), 614–620. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16630762

Burisch, J. (2014). Crohn's disease and ulcerative colitis. Occurrence, course and prognosis during the first year of disease in a European population-based inception cohort. Danish Medical Journal, 61(1), B4778. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=24393595

Burisch, J., Jess, T., Martinato, M., Lakatos, P. L., & -EpiCom, on behalf of E. (2013). The burden of inflammatory bowel disease in Europe. Journal of Crohn's and Colitis, 7(4), 322–337. https://doi.org/10.1016/j.crohns.2013.01.010

Burnett, S. J., Deelchand, V., Franklin, B. D., Moorthy, K., & Vincent, C. (2011). Missing Clinical Information in NHS hospital outpatient clinics: prevalence, causes and effects on patient care. BMC Health Services Research, 11(1), 114. https://doi.org/10.1186/1472-6963-11-114

Camilleri, M. (2014). Advances in understanding of bile acid diarrhea. Expert Review of

Gastroenterology & Hepatology, 8(1), 49–61. https://doi.org/10.1586/17474124.2014.851599

Cantoro, L., Di Sabatino, A., Papi, C., Margagnoni, G., Ardizzone, S., Giuffrida, P., … Kohn, A. (2017). The Time Course of Diagnostic Delay in Inflammatory Bowel Disease Over the Last Sixty Years: An Italian Multicentre Study. Journal of Crohn's and Colitis, 11(8), 975–980. https://doi.org/http://dx.doi.org/10.1093/ecco-jcc/jjx041

Carter, M. J., Lobo, A. J., & Travis, S. P. L. (2004). Guidelines for the management of inflammatory bowel disease in adults. Gut, 53(suppl 5), v1 LP-v16. https://doi.org/10.1136/gut.2004.043372

Castiglione, F., Diaferia, M., Morace, F., Labianca, O., Meucci, C., Cuomo, A., … Rispo, A. (2012). Risk factors for inflammatory bowel diseases according to the "hygiene hypothesis": a case-control, multi-centre, prospective study in Southern Italy. Journal of Crohn's & Colitis, 6(3), 324–329. https://doi.org/10.1016/j.crohns.2011.09.003

Chang, C.-W., Wong, J.-M., Tung, C.-C., Shih, I.-L., Wang, H.-Y., & Wei, S.-C. (2015). Intestinal stricture in Crohn's disease. Intestinal Research, 13(1ne), 19–26. https://doi.org/https://dx.doi.org/10.5217/ir.2015.13.1.19

Childers, R. E., Eluri, S., Vazquez, C., Weise, R. M., Bayless, T. M., & Hutfless, S. (2014). Family history of inflammatory bowel disease among patients with ulcerative colitis: a systematic review and meta-analysis. Journal of Crohn's & Colitis, 8(11), 1480–1497. https://doi.org/10.1016/j.crohns.2014.05.008

Colman, R. J., & Rubin, D. T. (2014). Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. Journal of Crohn's and Colitis, 8(12), 1569–1581. https://doi.org/10.1016/j.crohns.2014.08.006

Cosnes, J., Gower-Rousseau, C., Seksik, P., & Cortot, A. (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology, 140(6), 1785–1794. https://doi.org/https://dx.doi.org/10.1053/j.gastro.2011.01.055

Creswell, J.W. and Plano Clark, V.L. (2011) Designing and Conducting Mixed Methods Research. 2nd Edition, Sage Publications, Los Angeles.

Cross, R. K., Lapshin, O., & Finkelstein, J. (2008). Patient subjective assessment of drug side effects in inflammatory bowel disease. Journal of Clinical Gastroenterology, 42(3), 244–251. https://doi.org/10.1097/MCG.0b013e31802f19af

Das, K., Ghoshal, U. C., Dhali, G. K., Benjamin, J., Ahuja, V., & Makharia, G. K. (2009). Crohn's disease in India: a multicenter study from a country where tuberculosis is endemic. Digestive Diseases and Sciences, 54(5), 1099–1107. https://doi.org/https://dx.doi.org/10.1007/s10620-008-0469-6

Davis, J., Czerniski, B., Au, A., Adhikari, S., Farrell, I., & Fields, J. M. (2015). Diagnostic Accuracy of Ultrasonography in Retained Soft Tissue Foreign Bodies: A Systematic Review and Meta-analysis. Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine, 22(7), 777–787. https://doi.org/10.1111/acem.12714

Di Simone, A., & Riegler, G. (1987). The frequency of relapses as principle of evaluation in the follow-up of patients with ulcerative colitis. Acta Endoscopica, 17(4), 225–231. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=18125692

Dixon-Woods, M., & Critchley, S. (2000). Medical and lay views of irritable bowel syndrome. Family Practice, 17(2), 108–113. https://doi.org/10.1093/fampra/17.2.108

Doyle, Y., & Bull, A. (2000). Role of private sector in United Kingdom healthcare system. BMJ (Clinical Research Ed.), 321(7260), 563–565. https://doi.org/10.1136/bmj.321.7260.563

Duricova, D., Burisch, J., Jess, T., Gower-Rousseau, C., Lakatos, P. L., & ECCO-EpiCom, O. B. of. (2014). Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature☆. Journal of Crohn's and Colitis, 8(11), 1351–1361.

https://doi.org/10.1016/j.crohns.2014.05.006

Eaden, J. A., Abrams, K. R., & Mayberry, J. F. (2001). The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut, 48(4), 526–535.

Ephgrave, K. (2007). Extra-intestinal manifestations of Crohn's disease. Surgical Clinics of North America, 87(3), 673–680.

Etikan, I., Musa, S. A., & Alkassim, R. S. (2016). Comparison of convenience sampling and purposive sampling. American Journal of Theoretical and Applied Statistics, 5(1), 1–4.

Fetters, M. D., Curry, L. A., & Creswell, J. W. (2013). Achieving Integration in Mixed Methods Designs—Principles and Practices. Health Services Research, 48(6pt2), 2134–2156. https://doi.org/10.1111/1475-6773.12117

Finlay, L. (2002). "Outing" the researcher: the provenance, process, and practice of reflexivity. Qualitative Health Research, 12(4), 531–545. https://doi.org/10.1177/104973202129120052

Forbes, A., Escher, J., Hebuterne, X., Klek, S., Krznaric, Z., Schneider, S., … Bischoff, S. C. (2017). ESPEN guideline: Clinical nutrition in inflammatory bowel disease. Clinical Nutrition (Edinburgh, Scotland), 36(2), 321–347. https://doi.org/10.1016/j.clnu.2016.12.027

Foxworthy, D. M., & Wilson, J. A. (1985). Crohn's disease in the elderly. Prolonged delay in diagnosis. Journal of the American Geriatrics Society, 33(7), 492–495. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=4008848

Frandsen, M., Walters, J., & Ferguson, S. G. (2014). Exploring the Viability of Using Online Social Media Advertising as a Recruitment Method for Smoking Cessation Clinical Trials. Nicotine & Tobacco Research, 16(2), 247–251. Retrieved from http://dx.doi.org/10.1093/ntr/ntt157

Gallinger, Z., Ungaro, R., Colombel, J.-F., Sandler, R. S., & Chen, W. (2019). P030 DELAYED

DIAGNOSIS OF CROHN'S DISEASE IS COMMON AND ASSOCIATED WITH AN INCREASED RISK OF DISEASE COMPLICATIONS. Inflammatory Bowel Diseases, 25(Supplement_1), S14–S15. https://doi.org/10.1093/ibd/izy393.035

Gelinas, L., Pierce, R., Winkler, S., Cohen, I. G., Lynch, H. F., & Bierer, B. E. (2017). Using Social Media as a Research Recruitment Tool: Ethical Issues and Recommendations. The American Journal of Bioethics : AJOB, 17(3), 3–14. https://doi.org/10.1080/15265161.2016.1276644

Getnet, F., Demissie, M., Assefa, N., Mengistie, B., & Worku, A. (2017). Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. BMC Pulmonary Medicine, 17(1), 202. https://doi.org/10.1186/s12890-017-0551-y

Ghosh, S., & Mitchell, R. (2007). Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. Journal of Crohn's and Colitis, 1(1), 10–20. Retrieved from http://dx.doi.org/10.1016/j.crohns.2007.06.005

Gisbert, J. P., & Chaparro, M. (2014). Systematic review with meta-analysis: inflammatory bowel disease in the elderly. Alimentary Pharmacology & Therapeutics, 39(5), 459–477. https://doi.org/10.1111/apt.12616

Gklavas, A., Dellaportas, D., & Papaconstantinou, I. (2017). Risk factors for postoperative recurrence of Crohn's disease with emphasis on surgical predictors. Annals of Gastroenterology, 30(6), 598–612. https://doi.org/https://dx.doi.org/10.20524/aog.2017.0195

Glaser, B. G., Strauss, A. L., & Strutzel, E. (1968). The Discovery of Grounded Theory; Strategies for Qualitative Research. Nursing Research, 17(4). Retrieved from https://journals.lww.com/nursingresearchonline/Fulltext/1968/07000/The_Discovery_of_Grounded_Theory__Strategies_for.14.aspx

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. Journal of Family Medicine and Primary Care, 2(1), 9–14. https://doi.org/10.4103/2249-4863.109934

Gov.uk (2017 August). New home test kit for bowel cancer screening: what GPs need to know. Retrieved from: https://phescreening.blog.gov.uk/2017/08/04/new-home-test-kit-for-bowel-cancer-screening-what-gps-need-to-know/. Accessed on: 25.06.19

Greenwood-Van Meerveld, B., Johnson, A. C., & Grundy, D. (2017). Gastrointestinal Physiology and Function. Handbook of Experimental Pharmacology, 239, 1–16. https://doi.org/10.1007/164_2016_118

Griswold, K. S., Del Regno, P. A., & Berger, R. C. (2015). Recognition and Differential Diagnosis of Psychosis in Primary Care. American Family Physician, 91(12), 856–863.

Guandalini, S., & Sansotta, N. (2019). Probiotics in the Treatment of Inflammatory Bowel Disease. Advances in Experimental Medicine and Biology, 1125, 101–107. https://doi.org/10.1007/5584_2018_319

Gwee, K.-A. (2010). Post-Infectious Irritable Bowel Syndrome, an Inflammation-Immunological Model with Relevance for Other IBS and Functional Dyspepsia. Journal of Neurogastroenterology and Motility, 16(1), 30–34. https://doi.org/10.5056/jnm.2010.16.1.30

Haidich, A. B. (2010). Meta-analysis in medical research. Hippokratia, 14(Suppl 1), 29–37. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21487488

Hall, N. J., Rubin, G. P., Dougall, A., Hungin, A. P. S., & Neely, J. (2005). The Fight for 'Health-related Normality': A Qualitative Study of the Experiences of Individuals Living with Established Inflammatory Bowel Disease (IBD). Journal of Health Psychology, 10(3), 443–455. https://doi.org/10.1177/1359105305051433

Hamilton, W., Round, A., Sharp, D., & Peters, T. J. (2005). Clinical features of colorectal cancer

before diagnosis: a population-based case-control study. British Journal of Cancer, 93(4), 399–405. https://doi.org/10.1038/sj.bjc.6602714

Harper, P. H., Fazio, V. W., Lavery, I. C., Jagelman, D. G., Weakley, F. L., Farmer, R. G., & Easley, K. A. (1987). The long-term outcome in Crohn's disease. Diseases of the Colon and Rectum, 30(3), 174–179.

Harper, P., Mcauliffe, T., & Beeken, W. (1986). Crohn's Disease in the Elderly: A Statistical Comparison With Younger Patients Matched for Sex and Duration of Disease. Archives of Internal Medicine, 146(4), 753–755. https://doi.org/10.1001/archinte.1986.00360160189025

Hernan, M. A., Hernandez-Diaz, S., & Robins, J. M. (2004). A structural approach to selection bias. Epidemiology (Cambridge, Mass.), 15(5), 615–625.

Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. BMC Public Health, 13(1), 154. https://doi.org/10.1186/1471-2458-13-154

Heyman, M. B., Kirschner, B. S., Gold, B. D., Ferry, G., Baldassano, R., Cohen, S. A., … El-Serag, H. B. (2005). Children with early-onset inflammatory bowel disease (IBD): Analysis of a pediatric IBD consortium registry. The Journal of Pediatrics, 146(1), 35–40. https://doi.org/https://doi.org/10.1016/j.jpeds.2004.08.043

Holm, M., Saraswat, M., Joenväärä, S., Ristimäki, A., Haglund, C., & Renkonen, R. (2018). Colorectal cancer patients with different C-reactive protein levels and 5-year survival times can be differentiated with quantitative serum proteomics. PloS One, 13(4), e0195354–e0195354. https://doi.org/10.1371/journal.pone.0195354

Huang, B. L., Chandra, S., & Shih, D. Q. (2012). Skin manifestations of inflammatory bowel disease. Frontiers in Physiology, 3, 13. https://doi.org/https://dx.doi.org/10.3389/fphys.2012.00013

Hwang, J. M., & Varma, M. G. (2008). Surgery for inflammatory bowel disease. World Journal of Gastroenterology, 14(17), 2678–2690. https://doi.org/10.3748/wjg.14.2678

Jagosh, J., Donald Boudreau, J., Steinert, Y., Macdonald, M. E., & Ingram, L. (2011). The importance of physician listening from the patients' perspective: enhancing diagnosis, healing, and the doctor-patient relationship. Patient Education and Counseling, 85(3), 369–374. https://doi.org/10.1016/j.pec.2011.01.028

Jain, A., Sircar, S., Jain, M., & Adkar, S. (2012). Epidemiology of inflammatory bowel disease in central India-a five year experience. Indian Journal of Gastroenterology, 31(1 SUPPL. 1), A34–A35. https://doi.org/http://dx.doi.org/10.1007/s12664-012-0264-3

Jiwa, M., Skinner, P., Coker, A. O., Shaw, L., Campbell, M. J., & Thompson, J. (2006). Implementing referral guidelines: lessons from a negative outcome cluster randomised factorial trial in general practice. BMC Family Practice, 7(1), 65. https://doi.org/10.1186/1471-2296-7-65

Kallio, H., Pietilä, A.-M., Johnson, M., & Kangasniemi, M. (2016). Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. Journal of Advanced Nursing, 72(12), 2954–2965. https://doi.org/10.1111/jan.13031

Karlsen, T. H., Folseraas, T., Thorburn, D., & Vesterhus, M. (2017). Primary sclerosing cholangitis – a comprehensive review. Journal of Hepatology, 67(6), 1298–1323. https://doi.org/https://doi.org/10.1016/j.jhep.2017.07.022

Katikireddi, S. V., Egan, M., & Petticrew, M. (2015). How do systematic reviews incorporate risk of bias assessments into the synthesis of evidence? A methodological study. Journal of Epidemiology and Community Health, 69(2), 189 LP – 195. https://doi.org/10.1136/jech-2014-204711

Kedia, S., Ahuja, V., & Tandon, R. (2014). Management of acute severe ulcerative colitis. In World journal of gastrointestinal pathophysiology (Vol. 5). https://doi.org/10.4291/wjgp.v5.i4.579

Khalili, H., Chan, S. S. M., Lochhead, P., Ananthakrishnan, A. N., Hart, A. R., & Chan, A. T. (2018). The role of diet in the aetiopathogenesis of inflammatory bowel disease. Nature Reviews. Gastroenterology & Hepatology, 15(9), 525–535. https://doi.org/10.1038/s41575-018-0022-9

Khor, B., Gardet, A., & Xavier, R. J. (2011). Genetics and pathogenesis of inflammatory bowel disease. Nature, 474, 307. Retrieved from https://doi.org/10.1038/nature10209

Klag, T., Goetz, M., Stange, E. F., & Wehkamp, J. (2015). Medical Therapy of Perianal Crohn's Disease. Visceral Medicine, 31(4), 265–272. https://doi.org/10.1159/000434664

Koshiaris, C., Oke, J., Abel, L., Nicholson, B. D., Ramasamy, K., & Van den Bruel, A. (2018). Quantifying intervals to diagnosis in myeloma: a systematic review and meta-analysis. BMJ Open, 8(6), e019758. https://doi.org/10.1136/bmjopen-2017-019758

Kotze, P. G., Shen, B., Lightner, A., Yamamoto, T., Spinelli, A., Ghosh, S., & Panaccione, R. (2018). Modern management of perianal fistulas in Crohn's disease: future directions. Gut, 67(6), 1181 LP – 1194. https://doi.org/10.1136/gutjnl-2017-314918

Kozyraki, R., & Cases, O. (2013). Vitamin B12 absorption: Mammalian physiology and acquired and inherited disorders. Biochimie, 95(5), 1002–1007. https://doi.org/https://doi.org/10.1016/j.biochi.2012.11.004

Kyle, J. (1971). The early diagnosis of chronic Crohn's disease. Scottish Medical Journal, 16(3), 197–201. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=5557057

Langan, R. C., Gotsch, P. B., Krafczyk, M. A., & Skillinge, D. D. (2007). Ulcerative colitis: diagnosis and treatment. American Family Physician, 76(9), 1323–1330.

Langholz, E., Munkholm, P., Nielsen, O. H., Kreiner, S., & Binder, V. (1991). Incidence and prevalence of ulcerative colitis in Copenhagen County from 1962 to 1987. Scandinavian

Journal of Gastroenterology, 26(12), 1247–1256. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1763295

Lasch, K., Liu, S., Ursos, L., Mody, R., King-Concialdi, K., DiBonaventura, M., … Dubinsky, M. (2016). Gastroenterologists' Perceptions Regarding Ulcerative Colitis and Its Management: Results from a Large-Scale Survey. Advances in Therapy, 33(10), 1715–1727. Retrieved from https://link.springer.com/content/pdf/10.1007%2Fs12325-016-0393-7.pdf

Lee, C. K., & Melmed, G. Y. (2017). Multidisciplinary Team-Based Approaches to IBD Management: How Might "One-Stop Shopping" Work for Complex IBD Care? The American Journal of Gastroenterology, 112(6), 825–827. https://doi.org/10.1038/ajg.2017.124

Lee, D.-W., Koo, J. S., Choe, J. W., Suh, S. J., Kim, S. Y., Hyun, J. J., … Lee, S. W. (2017). Diagnostic delay in inflammatory bowel disease increases the risk of intestinal surgery. World Journal of Gastroenterology, 23(35), 6474–6481. https://doi.org/https://dx.doi.org/10.3748/wjg.v23.i35.6474

Lee, F. I., & Giaffer, M. (1987). Crohn's disease of late onset in Blackpool. Postgraduate Medical Journal, 63(740), 471–473. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=17080366

Lenicek, M., Duricova, D., Komarek, V., Gabrysova, B., Lukas, M., Smerhovsky, Z., & Vitek, L. (2011). Bile acid malabsorption in inflammatory bowel disease: Assessment by serum markers. Inflammatory Bowel Diseases, 17(6), 1322–1327. https://doi.org/10.1002/ibd.21502

Levine, J. S., & Burakoff, R. (2011). Extraintestinal manifestations of inflammatory bowel disease. Gastroenterology & Hepatology, 7(4), 235–241. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21857821

Li, Y., Ren, J., Wang, G., Gu, G., Wu, X., Ren, H., … Li, J. (2015). Diagnostic delay in Crohn's disease is associated with increased rate of abdominal surgery: A retrospective study in Chinese patients. Digestive and Liver Disease, 47(7), 544–548. https://doi.org/https://dx.doi.org/10.1016/j.dld.2015.03.004

Liddle, J., Roddy, E., Mallen, C. D., Hider, S. L., Prinjha, S., Ziebland, S., & Richardson, J. C. (2015). Mapping patients' experiences from initial symptoms to gout diagnosis: a qualitative exploration. BMJ Open, 5(9), e008323. https://doi.org/10.1136/bmjopen-2015-008323

Lin, W.-C., Chang, C.-W., Chu, C.-H., Shih, S.-H., & Wang, H.-Y. (2015). Older adults with late-onset ulcerative colitis: A single-center study. Journal of Gastroenterology and Hepatology (Australia), 30(SUPPL. 4), 42–43. https://doi.org/http://dx.doi.org/10.1111/jgh.13188

Lind, E., Fausa, O., Elgjo, K., & Gjone, E. (1985). Crohn's disease. Clinical manifestations. Scandinavian Journal of Gastroenterology, 20(6), 665–670. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=4035286

Loftus, E. V. J. (2004). Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology, 126(6), 1504–1517.

Lohsiriwat, V. (2012). Hemorrhoids: from basic pathophysiology to clinical management. World Journal of Gastroenterology, 18(17), 2009–2017. https://doi.org/10.3748/wjg.v18.i17.2009

Luchini, C., Stubbs, B., Solmi, M., & Veronese, N. (2017). Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Anal, 5(4), 80–84.

Lunney, P., Middleton, K., Wang, R., Andrews, J., Kariyawasam, V., Peat, J., & Selinger, C. (2012). Smoking prevalence in inflammatory bowel diseases and its effects on disease course and surgery. Journal of Gastroenterology and Hepatology, 27(SUPPL. 4), 110.

https://doi.org/http://dx.doi.org/10.1111/j.1440-1746.2011.07251-6.x

Lynass, R., Pykhtina, O., & Cooper, M. (2012). A thematic analysis of young people's experience of counselling in five secondary schools in the UK. Counselling and Psychotherapy Research, 12(1), 53–62. https://doi.org/doi:10.1080/14733145.2011.580853

Maaser, C., Sturm, A., Vavricka, S. R., Kucharzik, T., Fiorino, G., Annese, V., … Stoker, J. (2018). ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. Journal of Crohn's and Colitis, 13(2), 144-164K. https://doi.org/10.1093/ecco-jcc/jjy113

Maconi, G., Orlandini, L., Asthana, A. K., Sciurti, R., Furfaro, F., Bezzio, C., … C., B. (2015). The impact of symptoms, irritable bowel syndrome pattern and diagnostic investigations on the diagnostic delay of Crohn's disease: A prospective study. Digestive and Liver Disease, 47(8), 646–651. https://doi.org/https://dx.doi.org/10.1016/j.dld.2015.04.009

Magro, F., Gionchetti, P., Eliakim, R., Ardizzone, S., Armuzzi, A., Barreiro-de Acosta, M., … Hindryckx, P. (2017). Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. Journal of Crohn's and Colitis, 11(6), 649–670.

Malalasekera, A., Nahm, S., Blinman, P. L., Kao, S. C., Dhillon, H. M., & Vardy, J. L. (2018). How long is too long? A scoping review of health system delays in lung cancer. European Respiratory Review : An Official Journal of the European Respiratory Society, 27(149). https://doi.org/10.1183/16000617.0045-2018

Mas-Moya, J., & Singhi, A. D. (2015). The gross pathology of inflammatory bowel disease. Diagnostic Histopathology, 21(7), 261–266. https://doi.org/https://doi.org/10.1016/j.mpdhp.2015.07.001

McMullan, C., Pinkney, T. D., Jones, L. L., Magill, L., Nepogodiev, D., Pathmakanthan, S., … Mathers, J. M. (2017). Adapting to ulcerative colitis to try to live a “normal” life: a qualitative study of patients’ experiences in the Midlands region of England. BMJ Open, 7(8), e017544. https://doi.org/10.1136/bmjopen-2017-017544

Methley, A. M., Campbell, S., Chew-Graham, C., McNally, R., & Cheraghi-Sohi, S. (2014). PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Services Research, 14, 579. https://doi.org/10.1186/s12913-014-0579-0

Michael, M. D., Bálint, A., Lovász, B. D., Gulácsi, L., Strbák, B., Golovics, P. A., … Lakatos, P. L. (2014). Work disability and productivity loss in patients with inflammatory bowel diseases in Hungary in the era of biologics. The European Journal of Health Economics, 15(1), 121–128. https://doi.org/10.1007/s10198-014-0603-7

Mikocka-Walus, A., Power, M., Rook, L., Robins, G., & Committee, C. Y. W. P. (2018). What Do Participants of the Crohn’s and Colitis UK (CCUK) Annual York Walk Think of Their Inflammatory Bowel Disease Care? A Short Report on a Survey. Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates, 41(1), 59–64. https://doi.org/10.1097/SGA.0000000000000261

Mishler, E. (1986). Research Interviewing: Context and Narrative. USA: First Harvard University Press.

Mitchell, E., Macdonald, S., Campbell, N. C., Weller, D., & Macleod, U. (2008). Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. British Journal of Cancer, 98(1), 60–70. https://doi.org/10.1038/sj.bjc.6604096

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015

statement. Systematic Reviews, 4(1), 1. https://doi.org/10.1186/2046-4053-4-1

Molnár, T., Tiszlavicz, L., Gyulai, C., Nagy, F., & Lonovics, J. (2005). Clinical significance of granuloma in Crohn's disease. World Journal of Gastroenterology, 11(20), 3118–3121. https://doi.org/10.3748/wjg.v11.i20.3118

Moon, C. M., Jung, S.-A., Kim, S.-E., Song, H. J., Jung, Y., Ye, B. D., … Group, C. study. (2015). Clinical Factors and Disease Course Related to Diagnostic Delay in Korean Crohn's Disease Patients: Results from the CONNECT Study. PloS One, 10(12), e0144390. https://doi.org/http://dx.doi.org/10.1371/journal.pone.0144390

Moore, A., Grime, J., Campbell, P., & Richardson, J. (2013). Troubling stoicism: Sociocultural influences and applications to health and illness behaviour. Health (London, England : 1997), 17(2), 159–173. https://doi.org/10.1177/1363459312451179

Morgan, D. L. (2007). Paradigms Lost and Pragmatism Regained: Methodological Implications of Combining Qualitative and Quantitative Methods. Journal of Mixed Methods Research, 1(1), 48–76. https://doi.org/10.1177/2345678906292462

Mowat, C., Cole, A., Windsor, A., Ahmad, T., Arnott, I., Driscoll, R., … Bloom, S. (2011). Guidelines for the management of inflammatory bowel disease in adults. Gut, 60(5), 571 LP – 607. https://doi.org/10.1136/gut.2010.224154

Munkholm, P., Langholz, E., Nielsen, O. H., Kreiner, S., & Binder, V. (1992). Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962-87: a sixfold increase in incidence. Scandinavian Journal of Gastroenterology, 27(7), 609–614. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=22213309

Nambu, R., Hagiwara, S., Kubota, M., & Kagimoto, S. (2016). Difference between early onset and late-onset pediatric ulcerative colitis. Pediatrics International, 58(9), 862–866.

National Institute of Diabetes and Digestive and Kidney Diseases. NIDDK Image Library. Retrieved from: https://catalog.niddk.nih.gov/catalog/imagelibrary/searchresults.cfm?keyword=1537&type=keyword. Accessed on 09.02.19

National Institute of Health and Care Excellence. (2015 February). Inflammatory Bowel Disease. Retrieved from: https://www.nice.org.uk/guidance/qs81/chapter/Quality-statement-1-Specialist-assessment. Accessed on 01.07.19

National Institute of Health and Care Excellence. (2015 June). Suspected cancer: recognition and referral. Retrieved from: https://www.nice.org.uk/guidance/ng12. Accessed on 06.05.19.

National Institute of Health and Care Excellence. (2013 October). Bile acid malabsorption: colesevelam. Retrieved from: https://www.nice.org.uk/advice/esuom22/chapter/Key-points-from-the-evidence. Accessed on 18.01.19.

National Institute of Health and Care Excellence. (2013 October). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. Retrieved from: https://www.nice.org.uk/guidance/dg11. Accessed on 13.04.19.

Neal, R. D., Tharmanathan, P., France, B., Din, N. U., Cotton, S., Fallon-Ferguson, J., … Emery, J. (2015). Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. British Journal of Cancer, 112 Suppl, S92-107. https://doi.org/10.1038/bjc.2015.48

Nguyen, V. Q., Jiang, D., Hoffman, S. N., Guntaka, S., Mays, J. L., Wang, A., … Sorrentino, D. (2017). Impact of Diagnostic Delay and Associated Factors on Clinical Outcomes in a U.S. Inflammatory Bowel Disease Cohort. Inflammatory Bowel Diseases, 23(10), 1825–1831. https://doi.org/https://dx.doi.org/10.1097/MIB.0000000000001257

Novacek, G., Gröchenig, H. P., Haas, T., Wenzl, H., Steiner, P., Koch, R., … (ATISG), A. I. B. D. S. G. (2019). Diagnostic delay in patients with inflammatory bowel disease in Austria. Wiener

Klinische Wochenschrift, 131(5), 104–112. https://doi.org/10.1007/s00508-019-1451-3

Novick, G. (2008). Is there a bias against telephone interviews in qualitative research? Research in Nursing & Health, 31(4), 391–398.

Osei, E., Akweongo, P., & Binka, F. (2015). Factors associated with DELAY in diagnosis among tuberculosis patients in Hohoe Municipality, Ghana. BMC Public Health, 15, 721. https://doi.org/10.1186/s12889-015-1922-z

Oude Munnink, B. B., & van der Hoek, L. (2016). Viruses Causing Gastroenteritis: The Known, The New and Those Beyond. Viruses, 8(2), 42. https://doi.org/10.3390/v8020042

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4.

Paine, E. R. (2014). Colonoscopic evaluation in ulcerative colitis. Gastroenterology Report, 2(3), 161–168. https://doi.org/10.1093/gastro/gou028

Pannucci, C. J., & Wilkins, E. G. (2010). Identifying and avoiding bias in research. Plastic and Reconstructive Surgery, 126(2), 619–625. https://doi.org/10.1097/PRS.0b013e3181de24bc

Parente, J. M. L., Coy, C. S. R., Campelo, V., Parente, M. P. P. D., Costa, L. A., da Silva, R. M., … Zeitune, J. M. R. (2015). Inflammatory bowel disease in an underdeveloped region of Northeastern Brazil. World Journal of Gastroenterology, 21(4), 1197–1206. https://doi.org/https://dx.doi.org/10.3748/wjg.v21.i4.1197

Parsonage, R. K., Hiscock, J., Law, R.-J., & Neal, R. D. (2017). Patient perspectives on delays in diagnosis and treatment of cancer: a qualitative analysis of free-text data. British Journal of General Practice, 67(654), e49 LP-e56. https://doi.org/10.3399/bjgp16X688357

Patel, K., Doulias, T., Hoad, T., Lee, C., & Alberts, J. C. (2016). Primary-to-secondary care referral experience of suspected colorectal malignancy in young adults. Annals of the Royal College of

Surgeons of England, 98(5), 308–313. https://doi.org/10.1308/rcsann.2016.0123

Patel, R., Chang, T., Greysen, S. R., & Chopra, V. (2015). Social Media Use in Chronic Disease: A Systematic Review and Novel Taxonomy. The American Journal of Medicine, 128(12), 1335–1350. https://doi.org/https://doi.org/10.1016/j.amjmed.2015.06.015

Pellino, G., Sciaudone, G., Selvaggi, F., Riegler, G., G., P., G., S., & F., S. (2015). Delayed diagnosis is influenced by the clinical pattern of Crohn's disease and affects treatment outcomes and quality of life in the long term: a cross-sectional study of 361 patients in Southern Italy. European Journal of Gastroenterology and Hepatology, 27(2), 175–181. https://doi.org/http://dx.doi.org/10.1097/MEG.0000000000000244

Ponder, A., & Long, M. D. (2013). A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clinical Epidemiology, 5, 237–247. https://doi.org/10.2147/CLEP.S33961

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., … Duffy, S. (2006). Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC Methods Programme. https://doi.org/10.13140/2.1.1018.4643

Prior, J. A., Ranjbar, H., Belcher, J., Mackie, S. L., Helliwell, T., Liddle, J., & Mallen, C. D. (2017). Diagnostic delay for giant cell arteritis – a systematic review and meta-analysis. BMC Medicine, 15(1), 120. https://doi.org/10.1186/s12916-017-0871-z

Ray, G. (2016). Inflammatory bowel disease in India - Past, present and future. World Journal of Gastroenterology, 22(36), 8123–8136. https://doi.org/10.3748/wjg.v22.i36.8123

Reed, K. K., & Wickham, R. (2009). Review of the Gastrointestinal Tract: From Macro to Micro. Seminars in Oncology Nursing, 25(1), 3–14. https://doi.org/https://doi.org/10.1016/j.soncn.2008.10.002

Rehfeld, A., Nylander, M., & Karnov, K. (2017). The Digestive System II: The Associated Organs BT -

Compendium of Histology: A Theoretical and Practical Guide (A. Rehfeld, M. Nylander, & K. Karnov, eds.). https://doi.org/10.1007/978-3-319-41873-5_22

Reinisch, S., Schweiger, K., Pablik, E., Collet-Fenetrier, B., Peyrin-Biroulet, L., Alfaro, I., … Reinisch, W. (2016). An index with improved diagnostic accuracy for the diagnosis of Crohn's disease derived from the Lennard-Jones criteria. Alimentary Pharmacology & Therapeutics, 44(6), 601–611. https://doi.org/10.1111/apt.13727

Ricci, C., Lanzarotto, F., & Lanzini, A. (2008). The multidisciplinary team for management of inflammatory bowel diseases. Digestive and Liver Disease, 40, S285–S288. https://doi.org/https://doi.org/10.1016/S1590-8658(08)60539-3

Rispo, A., Imperatore, N., Testa, A., Nardone, O. M., Luglio, G., Caporaso, N., & Castiglione, F. (2018). Diagnostic Accuracy of Ultrasonography in the Detection of Postsurgical Recurrence in Crohn's Disease: A Systematic Review with Meta-analysis. Inflammatory Bowel Diseases, 24(5), 977–988. https://doi.org/10.1093/ibd/izy012

Romberg-Camps, M. J. L., Hesselink-van de Kruijs, M. A. M., Schouten, L. J., Dagnelie, P. C., Limonard, C. B., Kester, A. D. M., … M.G.V.M., R. (2009). Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991-2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. Journal of Crohn's and Colitis, 3(2), 115–124. https://doi.org/https://dx.doi.org/10.1016/j.crohns.2008.12.002

Rosen, M. J., Dhawan, A., & Saeed, S. A. (2015). Inflammatory Bowel Disease in Children and Adolescents. JAMA Pediatrics, 169(11), 1053–1060. https://doi.org/10.1001/jamapediatrics.2015.1982

Roth, L., Chande, N., Ponich, T., & Roth, M. (2010). Predictors of disease severity in ulcerative colitis patients from Southwestern Ontario. World Journal of Gastroenterology, 16(2), 232–236. https://doi.org/http://dx.doi.org/10.3748/wjg.v16.i2.232

Sackett, D. L. (1997). Evidence-based medicine. Seminars in Perinatology, 21(1), 3–5. https://doi.org/https://doi.org/10.1016/S0146-0005(97)80013-4

Saro Gismera, C., Riestra Menendez, S., Sanchez Fernandez, R., Milla Crespo, A., Lacort Fernandez, M., Arguelles Fernandez, G., … Lombrana, J. L. S. (2003). [Epidemiology in inflammatory bowel disease in five areas of Asturias. Spain]. Anales de medicina interna (Madrid, Spain : 1984), 20(5), 232–238.

Sategna-Guidetti, C., & Marucco, E. (1990). [Clinical characteristics of 153 patients with Crohn's disease. Presentation of a Turin case series]. Recenti Progressi in Medicina, 81(6), 435–439. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=21779700

Satsangi, J., Silverberg, M. S., Vermeire, S., & Colombel, J.-F. (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut, 55(6), 749–753. https://doi.org/10.1136/gut.2005.082909

Saunders, B., Kitzinger, J., & Kitzinger, C. (2014). Anonymising interview data: challenges and compromise in practice. Qualitative Research, 15(5), 616–632. https://doi.org/10.1177/1468794114550439

Saunders, B., Sim, J., Kingstone, T., Baker, S., Waterfield, J., Bartlam, B., … Jinks, C. (2018). Saturation in qualitative research: exploring its conceptualization and operationalization. Quality & Quantity, 52(4), 1893–1907. https://doi.org/10.1007/s11135-017-0574-8

Sawczenko, A., & Sandhu, B. (2003). Presenting features of inflammatory bowel disease in Great Britain and Ireland. Archives of Disease in Childhood, 88(11), 995–1000. https://doi.org/http://dx.doi.org/10.1136/adc.88.11.995

Schmidt, C., Ahmad, T., Tulassay, Z., Baumgart, D. C., Bokemeyer, B., Howaldt, S., … Group, the A.

S. (2016). Ferric maltol therapy for iron deficiency anaemia in patients with inflammatory bowel disease: long-term extension data from a Phase 3 study. Alimentary Pharmacology & Therapeutics, 44(3), 259–270. https://doi.org/10.1111/apt.13665

Schroeder, K. W., Tremaine, W. J., & Ilstrup, D. M. (1987). Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med, 317. https://doi.org/10.1056/NEJM198712243172603

Sehgal, R., & Koltun, W. (2010). Scoring systems in inflammatory bowel disease. In Expert review of gastroenterology & hepatology (Vol. 4). https://doi.org/10.1586/egh.10.40

Shapp, A. (2014). Variation in the use of Twitter hashtags. New York University.

Shefer, G., Henderson, C., Howard, L. M., Murray, J., & Thornicroft, G. (2014). Diagnostic overshadowing and other challenges involved in the diagnostic process of patients with mental illness who present in emergency departments with physical symptoms--a qualitative study. PloS One, 9(11), e111682–e111682. https://doi.org/10.1371/journal.pone.0111682

Singh, P., Teal, T. K., Marsh, T. L., Tiedje, J. M., Mosci, R., Jernigan, K., … Manning, S. D. (2015). Intestinal microbial communities associated with acute enteric infections and disease recovery. Microbiome, 3(1), 45. https://doi.org/10.1186/s40168-015-0109-2

Smith, J., & Noble, H. (2014). Bias in research. Evidence-Based Nursing, 17(4), 100–101. https://doi.org/10.1136/eb-2014-101946

Stiemsma, L. T., Reynolds, L. A., Turvey, S. E., Finlay, B. B., L.T., S., L.A., R., & S.E., T. (2015). The hygiene hypothesis: current perspectives and future therapies. ImmunoTargets and Therapy, 4, 143–157. https://doi.org/http://dx.doi.org/10.2147/ITT.S61528

Szanto, K., Nyari, T., Balint, A., Bor, R., Milassin, A., Rutka, M., … Molnar, T. (2018). Biological therapy and surgery rates in inflammatory bowel diseases - Data analysis of almost 1000 patients from a Hungarian tertiary IBD center. PloS One, 13(7), e0200824.

https://doi.org/https://dx.doi.org/10.1371/journal.pone.0200824

Tabibian, N., Swehli, E., Boyd, A., Umbreen, A., & Tabibian, J. H. (2017). Abdominal adhesions: A practical review of an often overlooked entity. Annals of Medicine and Surgery (2012), 15, 9–13. https://doi.org/10.1016/j.amsu.2017.01.021

Taghavi, A., Safarpour, A., & Hoseini, S. (2013). Epidemiology of inflammatory bowel diseases (IBD) in Iran: A review of 740 patients in southern Iran. Journal of Crohn's and Colitis, 7(SUPPL.1), S269. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=70992176

Tan, M., Holloway, R. H., Lange, K., & Andrews, J. M. (2012). General practitioners' knowledge of and attitudes to inflammatory bowel disease. Internal Medicine Journal, 42(7), 801–807. https://doi.org/10.1111/j.1445-5994.2011.02586.x

Targownik, L. E., Bernstein, C. N., & Leslie, W. D. (2013). Inflammatory bowel disease and the risk of osteoporosis and fracture. Maturitas, 76(4), 315–319. https://doi.org/https://doi.org/10.1016/j.maturitas.2013.09.009

Thia, K. T., Loftus, E. V. J., Sandborn, W. J., & Yang, S.-K. (2008). An update on the epidemiology of inflammatory bowel disease in Asia. The American Journal of Gastroenterology, 103(12), 3167–3182. https://doi.org/10.1111/j.1572-0241.2008.02158.x

Thomas, G., Rhodes, J., Green, J. T., & Richardson, C. (2000). Role of smoking in inflammatory bowel disease: implications for therapy. Postgraduate Medical Journal, 76(895), 273 LP – 279. https://doi.org/10.1136/pmj.76.895.273

Timmer, A., Behrens, R., Buderus, S., Findeisen, A., Hauer, A., KM, K., … P., R. (2011). Childhood Onset Inflammatory Bowel Disease: Predictors of Delayed Diagnosis from the CEDATA German-Language Pediatric Inflammatory Bowel Disease Registry. Journal of Pediatrics,

158(3), 467. https://doi.org/http://dx.doi.org/10.1016/j.jpeds.2010.09.014

Tremaine, W. J. (2011). Diagnosis and treatment of indeterminate colitis. Gastroenterology & Hepatology, 7(12), 826–828. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22347823

Urquhart, C. (2012). Grounded theory for qualitative research: A practical guide. Sage.

US National Library of Medicine (2019, April). Medline: Description of the database. Retrieved from: https://www.nlm.nih.gov/bsd/medline.html. Accessed on 07.12.18

van Duin, D. (2011). Diagnostic Challenges and Opportunities in Older Adults With Infectious Diseases. Clinical Infectious Diseases, 54(7), 973–978. https://doi.org/10.1093/cid/cir927

Vavricka, S. R., Schoepfer, A., Scharl, M., Lakatos, P. L., Navarini, A., & Rogler, G. (2015). Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflammatory Bowel Diseases, 21(8), 1982–1992. Retrieved from http://dx.doi.org/10.1097/MIB.0000000000000392

Vavricka, S. R., Spigaglia, S. M., Rogler, G., Pittet, V., Michetti, P., Felley, C., … M., F. (2012). Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflammatory Bowel Diseases, 18(3), 496–505. https://doi.org/https://dx.doi.org/10.1002/ibd.21719

Verhagen, L. M., Kapinga, R., & van Rosmalen-Nooijens, K. A. W. L. (2010). Factors underlying diagnostic delay in tuberculosis patients in a rural area in Tanzania: a qualitative approach. Infection, 38(6), 433–446. https://doi.org/10.1007/s15010-010-0051-y

Verstockt, B., Smith, K. G., & Lee, J. C. (2018). Genome-wide association studies in Crohn's disease: Past, present and future. Clinical & Translational Immunology, 7(1), e1001–e1001. https://doi.org/10.1002/cti2.1001

Vítek, L. (2014). Bile Acid Malabsorption in Inflammatory Bowel Disease. Inflammatory Bowel

Diseases, 21(2), 476–483. https://doi.org/10.1097/MIB.0000000000000193

Waljee, A. K., Rogers, M. A. M., Lin, P., Singal, A. G., Stein, J. D., Marks, R. M., … Nallamothu, B. K. (2017). Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ, 357, j1415. https://doi.org/10.1136/bmj.j1415

Walter, F., Webster, A., Scott, S., & Emery, J. (2012). The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis. Journal of Health Services Research & Policy, 17(2), 110–118. https://doi.org/10.1258/jhsrp.2011.010113

Weaver, K., Ronn MS, A., Melkus, G., D'Eramo EdD, C.-N., Henderson, W., & PhD, M. S. N. (2017). Irritable Bowel Syndrome. Am. J. Nurs., 117(6), 48–55. https://doi.org/10.1097/01.NAJ.0000520253.57459.01

Weizman, A. V, & Nguyen, G. C. (2011). Diverticular disease: epidemiology and management. Canadian Journal of Gastroenterology = Journal Canadien de Gastroenterologie, 25(7), 385–389. https://doi.org/10.1155/2011/795241

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). Newcastle-Ottawa quality assessment scale cohort studies. 2015-11-19]. Http://Www. Ohri. ca/Programs/Clinical_epidemiology/Oxford. Asp.

Wengrower, D., Goldin, E., Fich, A., & Granot, E. (1997). Crohn's disease in late adolescence: Acute onset or long-standing disease? Journal of Clinical Gastroenterology, 24(4), 224–226. https://doi.org/http://dx.doi.org/10.1097/00004836-199706000-00008

Whitaker, C., Stevelink, S., & Fear, N. (2017). The Use of Facebook in Recruiting Participants for Health Research Purposes: A Systematic Review. Journal of Medical Internet Research, 19(8), e290–e290. https://doi.org/10.2196/jmir.7071

Williams, P., Murchie, P., & Bond, C. (2019). Patient and primary care delays in the diagnostic pathway of gynaecological cancers: a systematic review of influencing factors. British Journal

of General Practice, 69(679), e106 LP-e111. https://doi.org/10.3399/bjgp19X700781

Wright, J. P. (1992). Factors influencing first relapse in patients with Crohn's disease. Journal of Clinical Gastroenterology, 15(1), 12–16. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1500656

Xavier, R. J., & Podolsky, D. K. (2007). Unravelling the pathogenesis of inflammatory bowel disease. Nature, 448, 427. Retrieved from https://doi.org/10.1038/nature06005

Yamamoto-Furusho, J. K., Fonseca-Camarillo, G., Furuzawa-Carballeda, J., Sarmiento-Aguilar, A., Barreto-Zuñiga, R., Martínez-Benitez, B., & Lara-Velazquez, M. A. (2018). Caspase recruitment domain (CARD) family (CARD9, CARD10, CARD11, CARD14 and CARD15) are increased during active inflammation in patients with inflammatory bowel disease. Journal of Inflammation, 15(1), 13. https://doi.org/10.1186/s12950-018-0189-4

Yamada, Y., Sugimoto, K., Yoshizawa, Y., Arai, Y., Otsuki, Y., Arai, T., … Hosoda, Y. (2018). Mesenteric inflammatory veno-occlusive disease occurring during the course of ulcerative colitis: a case report. BMC Gastroenterology, 18(1), 9. https://doi.org/10.1186/s12876-018-0737-7

Yang, S. K., Hong, W. S., Min, Y. I., Kim, H. Y., Yoo, J. Y., Rhee, P. L., … Kim, Y. K. (2000). Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong district, Seoul, Korea, 1986-1997. Journal of Gastroenterology and Hepatology (Australia), 15(9), 1037–1042. https://doi.org/http://dx.doi.org/10.1046/j.1440-1746.2000.02252.x

Yi, F., Chen, M., Huang, M., Li, J., Zhao, J., Li, L., & Xia, B. (2012). The trend in newly diagnosed Crohn's disease and extraintestinal manifestations of Crohn's disease in central China: a retrospective study of a single center. European Journal of Gastroenterology & Hepatology, 24(12). Retrieved from

https://journals.lww.com/eurojgh/Fulltext/2012/12000/The_trend_in_newly_diagnosed_Crohn_s_disease_and.11.aspx

Yuan, P., Bare, M. G., Johnson, M. O., & Saberi, P. (2014). Using online social media for recruitment of human immunodeficiency virus-positive participants: a cross-sectional survey. Journal of Medical Internet Research, 16(5), e117. https://doi.org/10.2196/jmir.3229

Zhang, M., Hong, L., Zhang, T., Lin, Y., Zheng, S., Zhou, X., … Zhong, J. (2016). Illness perceptions and stress: mediators between disease severity and psychological well-being and quality of life among patients with Crohn's disease. Patient Preference and Adherence, 10, 2387–2396. https://doi.org/10.2147/PPA.S118413

Appendices

Appendix 1 – Systematic Review Protocol

Arthritis Research UK Primary Care Centre

Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. A copy of this completed form will be available via the intranet to help others carrying out reviews in the future and to avoid duplicating work already undertaken in the Centre. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review and items should be adapted to fit the type of review that is being undertaken.

The template has been updated to include all the items from the PRISMA-P checklist (http://www.prisma-statement.org/Extensions/Protocols.aspx). All systematic reviews should be registered with PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/) unless the review is methodological.

Please complete the form in as much detail as possible for your review and email to Opeyemi Babatunde, o.babatunde@keele.ac.uk

7 Title of the review	Diagnostic Delay of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis
First reviewer	Eleanor Cross
Other reviewers (with role/contribution in the review)	James Prior (2nd reviewer and co-author), Benjamin Sunders (2nd reviewer and co-author), Adam Farmer (co-author)
Clinical Portfolio Group	N/A
Funding source	Conducted by funded student
PROSPERO registration number	CRD42018108886

Amendments to the protocol	To be completed

1. Background to review

7.3.1 Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim

Inflammatory Bowel Disease (IBD) includes both Crohn's Disease and Ulcerative Colitis, which are chronic conditions with a relapsing-remitting clinical course. Abnormal immune responses in the digestive tract is the suspected pathology of IBD. Crohn's disease can cause inflammation of any part of the digestive tract and symptoms include diarrhoea, weight loss, oral ulcers and perianal lesions. Ulcerative Colitis only affects the large bowel with the main symptoms being diarrhoea, abdominal pain and episodes of rectal bleeding. Though IBD can affect all ages, adolescents and young adults are most commonly affected and the condition has a drastic impact on the patient's life.

In order to alleviate symptoms and manage flares, quick diagnosis and prompt management is vital. Diagnosis is commonly confirmed by the histological analysis of colonoscopic biopsy. The aim of treatment is to reduce the aberrant immune responses in the digestive tract with steroids and other immunosuppressants. Surgery may be indicated in severe or stricturing disease.

This systematic review and qualitative research aims to examine the extent of delay between the onset of IBD symptoms experienced by patients and the final IBD diagnosis and examine characteristics related to the extent of delay. By aiming to determine when IBD diagnosis typically occurs, we can hopefully justify the need to improve the efficiency of the pathway of IBD diagnosis and thus management.

2. Specific objectives/questions the review will address
1. To explore the extent of diagnostic delay from IBD symptom onset to final IBD diagnosis 2. To examine whether the extent of diagnostic delay for IBD is associated with specific characteristics

3. a) Eligibility Criteria for including studies in the review If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading	
i. Population, or participants and conditions of interest	**Adult patients with a diagnosis of Inflammatory Bowel Disease**
ii. Interventions/Exposure/item of interest	**Clinician diagnosis of Inflammatory Bowel Disease**
iii. Comparisons or control groups, if any	**N/A**
iv. Outcomes of interest	**Time-period of diagnostic delay, with information about the impact of a diagnostic delay on the patient's clinical outcomes if such data is found from the search**
v. Setting	**Primary, secondary and tertiary care**
vi. Study designs	**All studies, including qualitative studies and literature reviews**

3. b) Criteria for excluding studies not covered in inclusion criteria
Exclusion criteria: Systematic reviews, conference abstracts, papers that are unavailable in English/unable to be translated. Papers where similar conditions to IBD are mentioned will be included if there Is specific mention to IBD in the title/abstract

4. Search methods	
Electronic databases & websites Please list all databases that are to be searched and include the interface (eg NHS HDAS, EBSCO, OVID etc) and date ranges searched for each. **NB All search strategies should be reviewed by Jo Jordan or Nadia Corp BEFORE searching begins**	Embase (Ovid), Medline (Ovid), CINAHL (HDAS). Search will not be limited by date ranges.
Other methods used for identifying relevant research ie contacting experts and reference checking, citation tracking	**7.4 Reference checking**
Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.	N/A

5. Methods of review	
How will search results be managed & documented? ie which reference management software, how duplicates dealt with	Results will be exported to Mendeley. Mendeley will be used to exclude duplicates, close duplicates will be assessed further by eye. From here, any identified duplicates will be deleted.
Selection process Number of reviewers, how agreements to be reached and disagreements dealt with, etc.	Using the selection criteria, the first reviewer (EC) will review papers by title, removing any duplicates and irrelevant articles. Then, the first & second reviewer (JP) will screen the remaining articles by their abstract. From the identified papers, the two reviewers (EC & JP) will independently select papers for inclusion based on the title and abstract content. EC, JP, AF, BS will independently include based on full-text. EC and JP will extract the relevant information from the studies to be included in the systematic review. Where an agreement needs to be made on study inclusion or exclusion, reviewers 1 and 2 will discuss to decide on final inclusion and exclusion.
Quality assessment Tools or checklists used with references or URLs, was this piloted? Is it to be carried out at same time as data extraction?	Select questions from the Newcastle-Ottawa tool will be used as a quality assessment tool.
How is data to be extracted? What information is to be collected on each included study? If databases or forms on Word or Excel are used, were these piloted and how is this recorded and by how many reviewers?	• Any reported time-period of diagnostic delay • Method of IBD diagnosis used in the study • Year of study • Demographic characteristics (eg- age and gender) • Sample size • Time period in which participants were recruited • Study setting (primary care, general population, secondary care) • How “delay” was quantified (i.e. delay in diagnosis was classed as the period of time between initial symptoms and final diagnosis, delay in treatment was classed as the period of time between initial symptoms and initial treatment etc)

Outcomes to be extracted & hierarchy/priority of measures ie which measure is preferred and if that is not available which is next in order of preference?	• Mean/median time period of delay in IBD diagnosis and related estimate range (i.e. SD, 95% CI, IQR)
Narrative synthesis Details of what methods, how synthesis will be done and by whom. Is the Narrative Synthesis Framework to be used?	An overview of the content of each article (study type, participants etc) and the diagnostic delays reported, including reasons for the delays and, where applicable, the impact on the participant.
Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.	In the instance that sufficient papers are sourced from the systematic review, a random effects model will be used in meta-analysis. If different methods of noting diagnostic delay after symptom onset are used, separate meta-analyses will be used.
Will the overall strength of evidence be assessed? If so, how? ie GRADE?	N/A

6. Presentation of results	
Outputs from review Papers and target journals, conference presentations, reports, etc	Paper

7.5 7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	**7.6 August - September**
Literature searching	**7.7 September - October**
Quality appraisal	**7.8 November**
Data extraction	**7.9 November**
Synthesis	**7.10 November - December**
Writing up	**7.11 December - January**

7.12 Support – please state if advice/training or personnel required at each stage	
SR overview	**7.13 N/A**
Protocol development	**7.14 Advice**
Literature searching	**7.15 Advice**
Quality appraisal	**7.16 N/A**
Data Extraction	**7.17 N/A**
Synthesis	**7.18 Advice (Statistical)**
Writing up	**7.19 N/A**

Please send your completed protocol to Opeyemi (see email below) as we would like to put examples on the Intranet.

The systematic review team are available to answer any queries or give advice on completing your review. Systematic review workshops are run at least once a year, or can be arranged on an ad hoc basis if needed by a group. Presentations from previous workshops can be found on the Centre's Intranet.

Opeyemi Babatunde – o.babatunde@keele.ac.uk

Jo Jordan – j.jordan@cphc.keele.ac.uk

Appendix 2- Search strategy used to source articles for the review

Exp inflammatory bowel diseases/

inflammatory bowel disease*.ti,ab,kw.

inflammatory bowel disorder*.ti,ab,kw.

ibd.ti,ab,kw.

crohn*.ti,ab.

ulcerative colitis*.ti,ab,kw.

inflam* colitis*.ti,ab,kw.

colitis/ or colitis, ulcerative/

diagnos* adj3 delay*.ti,ab,kw.

diagnos* adj3 lag*.ti,ab,kw.

diagnos* adj3 interval*.ti,ab,kw.

((late* or earl*) adj3 diagnos*).ti,ab,kw.

(health* adj3 seek*).ti,ab,kw.

(case* adj3 seek*).ti,ab,kw.

(case adj3 find*).ti,ab,kw.

(delay* adj3 consult*).ti,ab,kw.

(delay* adj3 detect*).ti,ab,kw.

(delay* adj3 interval*).ti,ab,kw.

(delay* adj3 refer*).ti,ab,kw.

(delay* adj3 treat*).ti,ab,kw.

Delayed diagnosis/

Early diagnosis/

Appendix 3- Example table used in the data extraction of included articles

Initials (EC,JP, BS,AF)	Author	Title	Publication Year	Country of Study	Study Design	Study Setting (primary/ secondary care)	No of Participants (incl. drop-outs)	Gender M:F	Age (Years)	Diagnosis (CD/UC)	Recruitment time	Length of Follow-Up	Inclusion/ Exclusion Criteria	Comments	Keys Symptoms at Diagnosis	Diagnostic Criteria Used	Method of Diagnosis	Definition of Diagnostic Delay (eg- Sx Onset to Dx)	Diagnostic Delay- Median (Range)	Diagnostic Delay- Mean (Range)
EC, JP	Kyle, J	The early diagnosis of chronic Crohn's disease	1971	Aberdeen, Scotland	Cross-sectional	Not reported	175 (10 excl.)	Samll bowel CD (54M:86F) Large bowel CD (12M:23F)		Small bowel CD= 140 Large Bowel CD= 35	1955-1969		Excl- Acute onset CD (10 pts)		Abdo pain (55%), diarrhoea, rectal bleeding. 20% other Sx- vomiting, swollen joints, spondylitis	Not reported	Stool toluidine, bloods results, sigmoidoscopy, barium enema	Onset of symptoms to diagnosis	6 mnths	19 mnths (1 day-30 yrs)
EC	Burisch, J	Crohn's disease and ulcerative colitis. Occurrence, course and prognosis…	2014	Europe (Eastern- 8) Europe (Western- 14)	Prospective Cohort Study	Secondary, outpatient	1515 adult	822:693 M:F- total **Eastern** (CD 63:42, UC 82:63, IC 4:2) **Western** (CD 220:210, UC 375:293, IC 78:83)	? Mean ? **Eastern=** CD 32 (15-78) UC 36 (18-81) IC 30 (20-34) **Western=** CD 38 (16-89) UC 39 (15-89) IC 38 (16-84)	**Eastern-** CD (105), UC (145), IC (16) **Western-** CD (430), UC (668), IC (161)	1/1/2010-31/12/2010	12 +/- 3 mnths, every 3rd mnth from Dx	incl- Meet "Copenhagen Diagnostic Criteria for IBD"	Aged >15yrs (Paed IBD= 45, UC=27, CD= 15, IBDU= 3)- separate from adult data		Copenhagen Diagnostic Criteria for IBD	Colonoscopy, sigmoidoscopy, [upper endoscopy (Western), BXR (Eastern)]	Onset of symptoms to diagnosis	**Eastern-** CD 3.4mnths (0-20y), UC 2.2m (0-5y), IC 2.7m (0-3y) **Western-** CD 4.6mnths (0-31y), UC 2.5m (0-21y), IC 2.4m (0-30y)	

Appendix 4- Newcastle-Ottawa Scale used to appraise the included cohort studies

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community*

b) somewhat representative of the average _____ in the community -

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort*

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (e.g, surgical records)*

b) structured interview*

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) *

b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment*

b) record linkage*

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) *

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for*

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select

an adequate %) follow up, or description provided of those lost) *

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

Appendix 5- Newcastle-Ottawa Scale used to appraise the included cross-sectional studies

Selection

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (nonrandom sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. **

b) Non-validated measurement tool, but the tool is available or described.*

c) No description of the measurement tool.

Comparability

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *

b) The study control for any additional factor. *

Outcome

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

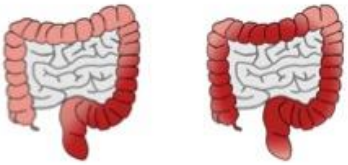
Appendix 6- Poster used to advertise the qualitative study on social media

Have you been diagnosed with Inflammatory Bowel Disease, Crohn's Disease or Ulcerative Colitis?

Did you experience a long wait from when your symptoms started to when you were diagnosed?

If so, you may be able to help us with our new research study

We are interested in hearing people's views and experiences of the delay take to receive a diagnosis of these conditions and the possible reasons for this



If you would like to help us by discussing this topic in a telephone interview, please contact Eleanor Cross to arrange a convenient time:

- Email- ibdresearchkeele@gmail.com
- Telephone- 01782 734847
- Twitter- IBDresearchKLE

Keele UNIVERSITY

Appendix 7- Cover letter sent to all individuals who expressed an interest in participating in the study

Thank you for already showing an interest in taking part in a new study being undertaken by researchers at the Research Institute for Primary Care and Health Sciences at Keele University.

We are trying to find out more about **Inflammatory Bowel Disease (IBD),** specifically why it can sometimes take a long time for patients to get a final diagnosis. We'd like to understand this problem better by interviewing you over the phone to discuss your experiences. Please see the enclosed Participant Information Sheet (version 5, dated 20/11/18) for further information regarding the research project and what it will involve you doing if you take part.

We hope that you will be able to spare some time for a telephone interview with our researcher, it should take approximately 30 minutes. The interview will be recorded, but **all of your answers will be dealt with in the strictest confidence.** We can also assure you that the answers you give, will not in any way, affect the health care you receive.

If you would still like to take part, we would be very grateful if you would fill in the enclosed consent form and sign it at the bottom (either by written signature, electronic signature or typing your name in full) . Please then return this to us either by email or using the pre-paid envelope provided as soon as you can. **You do not need a stamp.** Once we have received this our Research Assistant at Keele University, **Eleanor Cross** will phone you to arrange a convenient time for your telephone interview. However, if you would like to know more about this study, please contact, Eleanor on **01782 734847** or email ibdresearchkeele@gmail.com

Yours sincerely,

Dr James Prior
Research Fellow
Research Institute for Primary Care and Health Sciences
Keele University
Staffordshire, ST5 5BG

Appendix 8- Participant information letter sent to all individuals who expressed an interest in participating in the study

PARTICIPANT INFORMATION SHEET

Diagnostic Delay in Inflammatory Bowel Disease

You are being invited to take part in a research study. Before you decide whether to take part or not, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully.

What is the purpose of the study?

Inflammatory Bowel Disease (IBD) is a condition that can cause pain, cramps, swelling of the gut, bloody diarrhoea and tiredness. Patients with IBD can be well for long periods, but flares can come back. A delay in receiving a diagnosis of IBD can result in delayed treatment, worse symptoms and future complications. Keele University is carrying out a new research study to understand the reasons why the diagnosis of IBD can be delayed. We hope that understanding this problem better will allow us to reduce the amount of delay experienced by patients.

Why have I been invited?

You have been invited to take part because you have been identified as someone who has had a diagnosis of IBD in the past.

Do I have to take part?

No. Whether or not you take part in this research is up to you. If you do decide to take part, you are free to withdraw within a month of entering the study without giving a reason. A decision to withdraw, or a decision not to take part, will not affect your right to access health services at your general practice or elsewhere.

What happens if I decide to take part?

Agreeing to be in this study means that you will be asked to take part in a one-off telephone interview. During this interview, the researcher will ask you questions about your personal experience of the time between when your IBD symptoms started and finally receiving your IBD diagnosis, and how this final diagnosis was reached. The interview will last approximately 30 minutes. We just want to hear about your experiences, so there are no right or wrong answers. You do not need to do anything to prepare for the interview.

The interview will be sound-recorded. Following the interview, sound recordings will be sent for transcription, meaning the recording will be typed out to make a paper copy of the interview - called a transcript. Recordings will be sent via a secure upload system to Keele Clinical Trials Unit's supplier with whom there is a contract in place around confidentiality and security. The written copy will be returned encrypted, uploaded to the appropriate storage and deleted from email. All of this will be explained to you again at the beginning of the interview, and you will be asked to sign a consent form.

What are the possible benefits of taking part?

There will be no immediate benefits to you; however, we hope that the insight we gain from this research will lead to improvements in patient care, and hence help patients in the future.

What are the possible risks of taking part?

On the basis that the study involves participating in a telephone interview regarding your medical experiences, we do not anticipate any risks to you. Some of the questions asked regarding IBD may, however, invoke painful or distressing memories. If this is the case, the interview can be paused or stopped indefinitely. Please seek advice and support from your GP, NHS 111 or the Crohn's and Colitis UK charity (www.crohnsandcolitis.org.uk) if you feel distressed after the interview has occurred, or contact ourselves if you are unsure which services to use and we can be of help.

Will my taking part in this study be kept confidential?

Yes, the answers you give in the interview will be dealt with in **strictest confidence**. Each person who is interviewed will be given a study number, so the data from the study will not have any identifiable information, such as names and addresses, and cannot be traced back to you. Handling of data will be totally compliant with General Data Protection Regulation (GDPR). You can find out how we use your information at https://www.keele.ac.uk/informationgovernance/informationgovernanceforthepublic/

The paper transcript from the interview will be anonymised, which means it will not contain any information that would identify you. If you mention the names of people or places, these will be removed from the paper transcript. This anonymised

information will be kept and may be used in other research studies, but researchers who work with this data will not have access to your personal information. Quotations from your transcript may be used in reports, but it will not be possible for people to identify you.

How long will the answers to the study interview be stored for?

Your identifiable contact details will be stored in a secure place only until the end of the study. Members of staff from regulatory departments may require access to your records to check that the research has been carried out to a high standard. Therefore, anonymised interview content will be stored securely until 5 years after the end of the research. After this time the transcripts will be destroyed. All identifiable personal information such as your name and address will be destroyed at the end of the study period. This will ensure that personal data will not be stored for longer than is necessary (General Data Protection Regulation 2018).

What will happen if I don't want to carry on with this study?

You can withdraw from this study up to a month after being interviewed by contacting **Eleanor Cross,** the Research Assistant on **01782 734847** or by email (ibdresearchkeele@gmail.com). Withdrawing means that we would no longer contact you directly, but we would still keep and use the information you have provided up to the point of your withdrawal.

What will happen to the results of the research study?

The main findings from the study will be published in medical journals and will be used to improve understanding of diagnostic delay in IBD, which could have future implications for clinical care. A summary of the overall findings can be provided to you upon request.

Who is funding and organising the research?

The research is funded and organised by the Arthritis Research UK Primary Care Centre, at Keele University.

Who has reviewed the study?

Keele University Ethical Review Panel have approved this research study (Reference number: ***MH - 180002***)

Who should I contact if I would like further information?

If you have any questions, or would like further information about this study please contact **Eleanor Cross,** the Research Assistant on **01782 734847** or on e-mail address:

ibdresearchkeele@gmail.com If you have any general questions or concerns about taking part in research, you can also contact the Patient Advice and Liaison Service (PALS). You can ask your GP surgery, hospital or phone NHS 111 for details of your nearest PALS; further information about PALS is also available at the NHS Choices website (website link: http://www.nhs.uk/chq/Pages/1082.aspx?CategoryID=68&SubCategoryID=153).

You can also make a complaint using the formal complaints procedure at your GP Surgery.

What should I do now if I want to take part?

Please complete the consent form accompanying this information sheet and return to Eleanor, either via e-mail (ibdresearchkeele@gmail.com) or by the return envelope provided

Upon receipt of your consent form, Eleanor will get in touch with you to ask a few simple questions to check if you are eligible to take part and arrange a convenient time and date to conduct your telephone interview.

Thank you for taking time to read this information sheet.

Appendix 9- Consent form sent to all individuals who expressed an interest in participating in the study

Keele research ethics panel reference number: ***MH - 180002***

Centre Number:

Study Number:

Participant Identification Number for this study:

CONSENT FORM

Title of Project: Diagnostic Delay in Inflammatory Bowel Disease

Name of Research Assistant: Eleanor Cross

1. I confirm that I have read the information sheet dated 20/11/18 (version 5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time up to a month after my interview without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that anonymised information collected about me may be shared with other researchers. ☐
4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 10- Topic guide

Topic Guide: Patients

Diagnostic Delay in IBD Interview Topic Guide

Introduction

a. Check that participant has read and understood the patient information sheet.
b. Explain arrangements for: consent, recording, anonymity
c. Check patient's recollection of the process of receiving their diagnosis of IBD (this will have been asked initially when arranging the interview)
d. Confirm with patient through which service or organisation they learned of this study

Experience of period between symptom onset and diagnosis

e. How did initial symptoms present?
f. How did you interpret these symptoms?
g. Age at symptom onset
h. How long after initial symptom presentation did they contact their doctor?
i. At consultation, how were symptoms interpreted/what management plans/diagnoses were made?
j. How long after original consultation did diagnosis take?

How was final diagnosis reached

k. Diagnosed from original/first consultation/referral?
l. Diagnosed after worsening, or change of symptoms?
m. What happened at the referral appointments?
n. What investigations occurred?
o. What management was tried (right/wrong diagnosis made)?
p. Did patient feel they had to struggled/found it difficult to be referred/have symptoms taken seriously? (if mentioned by participant)
q. How did the patient feel before and after being diagnosed?
r. Age at diagnosis

Key factors of diagnostic delay

s. Main barriers to diagnosis perceived by patient (prompt patient to consider their own actions as barriers and barriers they experienced from healthcare side, specifically their GP or when in secondary care)

t. Personal impact of delayed diagnosis?
u. Does patient think symptoms/management may have been different if they'd received an earlier diagnosis?
v. Impact of condition on life
w. Further details regarding complications or narrative of diagnosis and disease progression

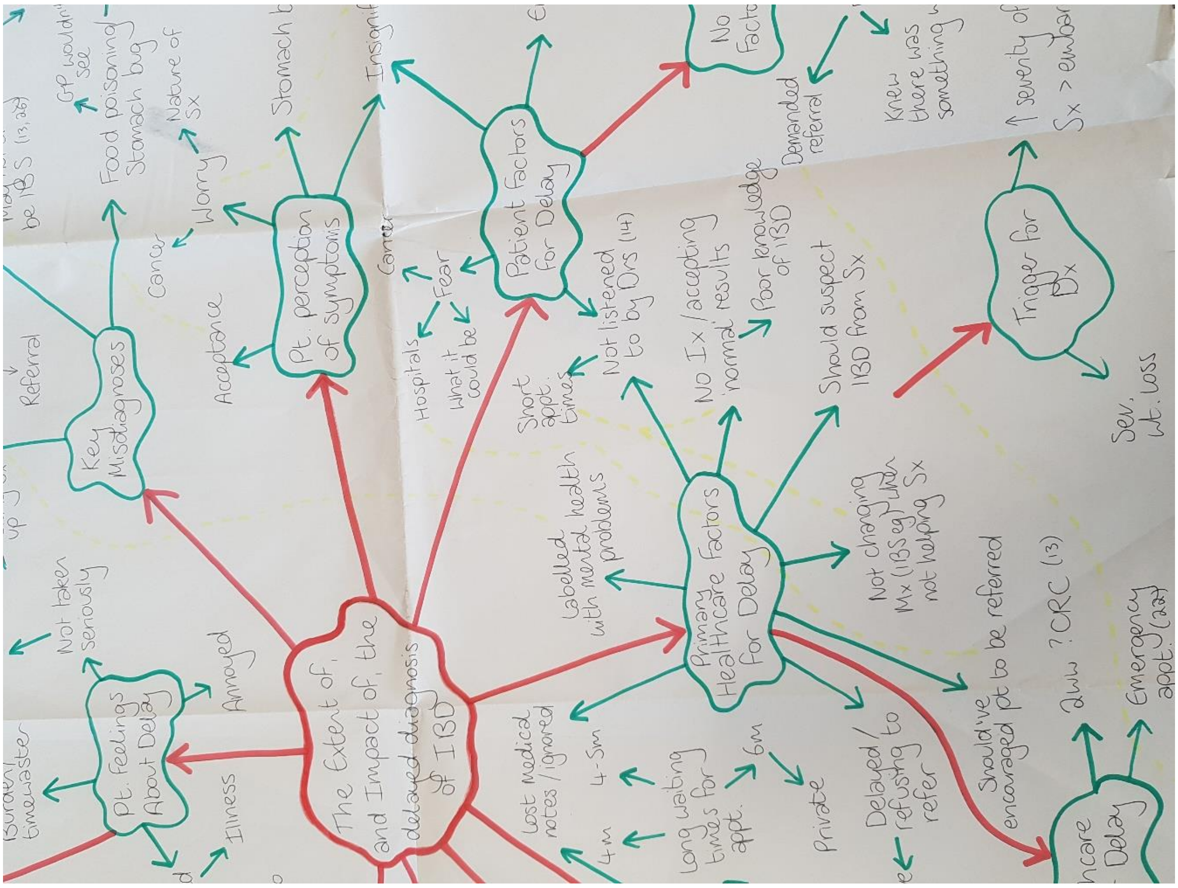
Clinical course of condition since diagnosis

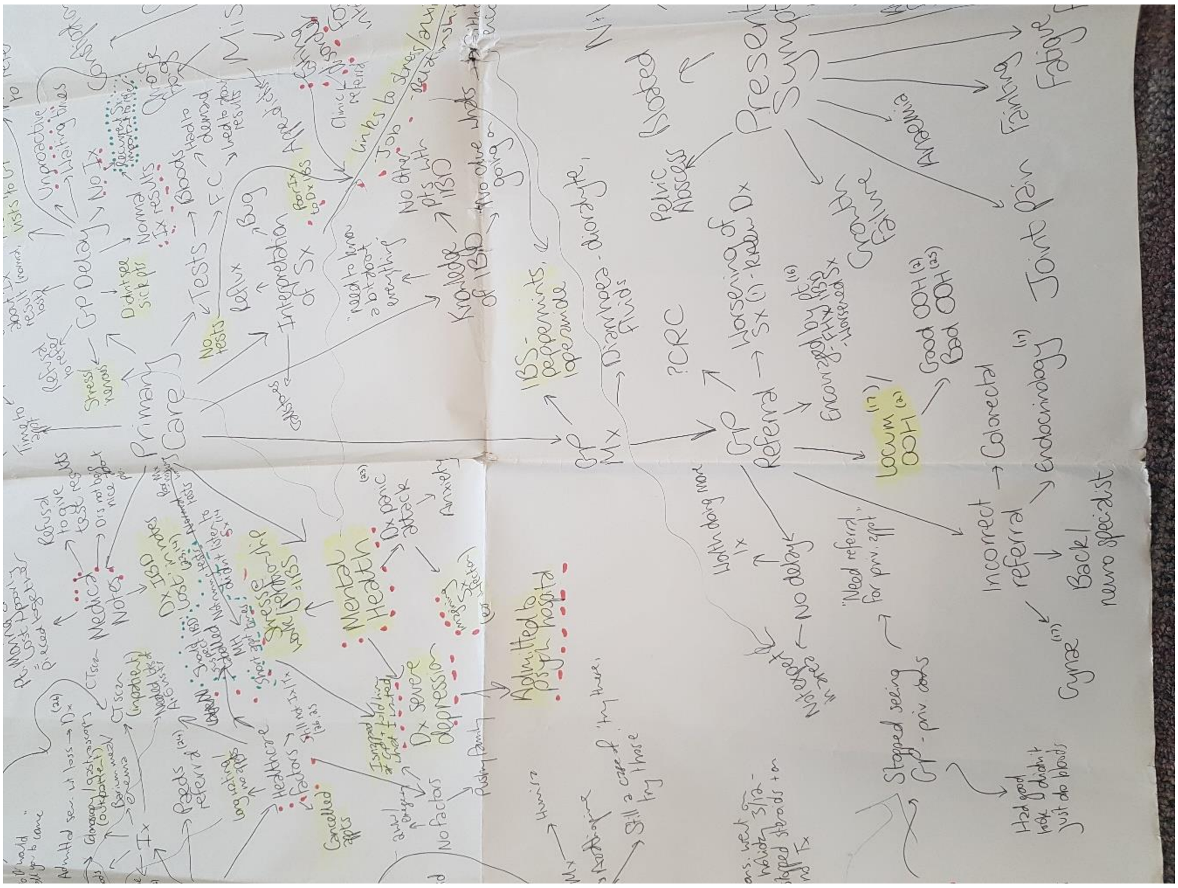
a. Has condition been well-managed since diagnosis? (brief overview)
b. How many flares has patient had- potential time interval
c. Medical and surgical management of condition
d. General wellbeing of patient

Close of discussion

a. Summary of discussion: any additional remarks?
b. Check consent is still in place.
c. Check if participant would like to receive a summary of the interview findings.
d. Emotional support

Appendix 11- Thematic maps


The Extent of, and Impact of, the delayed diagnosis of IBD
Pt. Feelings About Delay
Key Misdiagnoses
Pt. perception of symptoms
Patient Factors for Delay
Primary Healthcare Factors for Delay
Trigger for Dx


Primary Care
Mental Health
GP Referral

Appendix 12- Ethical approval for the qualitative research

16th October 2018

Dear James

PI: Eleanor Cross/James Prior
Title: Understanding the extent of, and reasons for, diagnostic delay in inflammatory bowel disease
Ref: ERP2402

Thank you for submitting your application for review. The proposal was reviewed by the Panel Chair. I am pleased to inform you that your application has been approved by the Ethics Review Panel.

If the fieldwork goes beyond the date stated in your application, or there are any amendments to your study you must submit an 'application to amend study' form to the ERP administrator at research.governance@keele.ac.uk. This form is available via https://www.keele.ac.uk/raise/researchsupport/projectassurance/researchethics/

If you have any queries please do not hesitate to contact me, in writing, via the ERP administrator, at research.governance@keele.ac.uk stating **Ref: ERP2402** in the subject line of the e-mail.

Yours sincerely
PP.

Dr Colin Rigby
Chair – Ethical Review Panel