ASSESSMENT OF INFLAMMATORY BOWEL DISEASE EPIDEMIOLOGY IN BARWON, VICTORIA: AN OBSERVATIONAL PROSPECTIVE POPULATION BASED STUDY

By

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A thesis submitted for the degree of
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This research thesis is dedicated to the loving memory of my Brother-in-law Tom Nicholson, who died tragically at the end of this research project. His life, spirit and positive attitude will always be remembered by our family.
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DOCTOR OF MEDICAL SCIENCE

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Solemnly and sincerely declare, in relation to the thesis entitled:

“ASSESSMENT OF INFLAMMATORY BOWEL DISEASE EPIDEMIOLOGY IN BARWON, VICTORIA: AN OBSERVATIONAL PROSPECTIVE POPULATION BASED STUDY”

(a) That work was done by me, personally

(b) Material has not been previously accepted in whole, or in part, for any other degree of diploma

Signature ........................................................... Date:...........................
Acknowledgements

There are many people who have supported this research project, without whom the study could not have been completed.

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Local IBD incidence rates, recent rate changes, disease phenotypes and clinical details of new IBD cases in Barwon

Local IBD prevalence rates, disease phenotypes and burden of care provided in General Practice

Longitudinal observation of a newly established IBD inception cohort; Three month outcome data of the Pilot Barwon IBD Registry

Conclusion

Directions for future epidemiology research
CHAPTER 1.

1.1 PROBLEM STATEMENT.

The medical condition inflammatory bowel disease (IBD) comprises two main types, Crohn’s disease (CD) and ulcerative colitis (UC). If complete diagnostic features for either CD or UC are not present, then a third clinical condition referred to as IBD unspecified (IBDU) has been defined. Collectively, these conditions are chronic immune mediated inflammatory diseases that have their primary activity within the gastrointestinal tract, but can also produce effects at extra-intestinal sites (Logan and Bowlus, 2010). The signs, symptoms and complications of these multisystem diseases can be complex. Our current understanding of aetiology, pathogenesis and the disease evolution of IBD is biased from an over representation of hospital-based patient cohorts. However, more recently, community or population-based research has emerged, revealing important new information regarding IBD risk-factors, community disease burden, and clinical factors able to predict aggressive disease course.

This thesis provides new and novel epidemiological insights into IBD in Australia. IBD incidence and prevalence rates have been calculated for the Barwon region, in South West Victoria, providing reliable population-based data reflecting the disease burden in this community. In addition, a pilot IBD registry has been successfully established. This community-based inception cohort has provided short-term disease-specific outcome data including surgical rates, medication use and complications. In the future, longitudinal study of this cohort will provide an opportunity for disease evolution in a population-based IBD to be studied, allowing for comparison with similarly designed international IBD cohorts.

Epidemiological data from Europe and North America show that the incidence and prevalence of IBD has increased rapidly over the last 50 years, with recent estimates that over 3.5 million people live with IBD in these regions alone (Logan and Bowlus, 2010) (Baumgart et al., 2011). A recent epidemiological study from New Zealand has demonstrated far higher incidence and prevalence rates for both Crohn’s disease and UC than previously estimated (Gearry et al., 2006). In Australia, disease burden estimates from 2007 suggested that over 61000 people were affected by IBD, with a predicted 1500 new cases being diagnosed each year (Access Economics Report, 2007). However, newer Australian data suggest that disease incidence and prevalence rates may have been grossly underestimated, suggesting local IBD rates higher than published international figures (Wilson et al., 2010). When compared to local disease rates for other chronic medical conditions, the revised data places IBD higher in prevalence than epilepsy, multiple sclerosis and schizophrenia, and equal to the local rates of type 1 diabetes (Wilson et al., 2010).

While the cause of IBD remains unknown, it is likely the result of a complex interplay between many factors (Engal and Neurath, 2010). It has been postulated that IBD occurs in genetically susceptible individuals who exhibit an abnormal interaction or response between particular environmental factors, the gut microbiota, and the gastrointestinal immune system (Engal and Neurath, 2010, Mayer, 2010). While the disease can be diagnosed at any stage of life, the onset of IBD occurs most
frequently between adolescence through to age 40 (Thia et al., 2008). In addition, it appears that the course of disease is more severe and disabling with onset at this younger age (Wolters et al., 2006). Illness during this stage of educational, psychosocial and professional development can have a significant impact on patients. Finally, while the true economic costs from IBD are difficult to estimate, Australian data suggest that when incorporating loss of productivity, direct health care costs, carer costs and cost associated with loss of well being, the economic burden is over 2.7 billion Australian dollars per year (Access Economics, 2007).

The clinical profiles of CD and UC are often quite different. The characteristic symptoms and signs of CD include chronic diarrhoea, abdominal pain, fatigue, weight loss, bleeding, fever, anaemia and peri-anal fistulae and abscesses (Stange et al., 2005). CD can affect any part of the length of the GI tract, although the terminal ileum and colon are most commonly involved. The disease can be complicated by the development of intestinal obstruction, perforation, fistula and abscess formation, in which case surgery is usually required. Conversely, UC only affects the colon, and frequently produces diarrhoea as the primary symptom. Rectal bleeding is also a very common feature of UC (Thoreson and Cullen, 2007). The chronic intestinal inflammation associated with either forms of IBD also predisposes to subsequent colo-rectal cancer development, often at a much younger age than the general population (Peyrin-Biroulet et al., 2011, Lakatos and Lakatos, 2008). Cancer surveillance programs are generally recommended for these patients.

Another challenging feature of IBD is the unpredictability of disease course. The behaviour of IBD can vary substantially from one individual to another. Generally, the condition waxes and wanes with episodes of disease flares followed by periods of remission, usually induced by medication or surgery (Loftus et al., 2002). A small subset of patients may present with very mild disease, and enter a prolonged period of remission with no active symptoms. For the majority of patients IBD is life long, and requires long term medication, multiple surgeries and prolonged medical care. However, most of the disease evolution studies in the literature have been conducted from tertiary referral centres with a very selective IBD population cohort, raising the possibility of a severity bias being introduced into the disease related observations. Patients requiring referral to tertiary centres are likely to have more severe disease. To date, no prospective comprehensive disease evolution studies of IBD have been conducted in an Australian population-based setting.

Thus, the true burden of IBD in Australia is currently poorly defined. Subsequently, there is a risk that insufficient health care resources are currently allocated to the care of this condition. To further define local disease burden, and to investigate the causes and observe disease evolution of newly diagnosed population-based IBD patients, community-based research into IBD is urgently needed in Australia. This premise forms the basis for the following thesis.

1.2 SCOPE OF THIS RESEARCH.

Firstly, we aim to determine the incidence of IBD over a 12-month period in a geographically defined Australian population, and to compare this to incidence rates obtained from the same region during 2007/2008.

Secondly, the prevalence rate of IBD in the same region will be calculated, producing Australia’s first prospective population-based IBD prevalence data.
Thirdly, we will create a population-based IBD registry through a pilot study incorporating all newly diagnosed, clinically-validated incident IBD cases. This cohort will form the basis for longitudinal observations to assess current IBD disease evolution in Australia, allowing identification of factors that may predict a more severe, complicated disease course and allow targeted therapy to those patients who may be at highest risk of disease progression.

1.3 STRUCTURE OF THIS THESIS.

A general background is first presented, before moving onto the main body of the thesis covering the original research work. Chapter 2 presents the findings of a comprehensive literature review, aiming to review IBD in general, with a focus on IBD epidemiological concepts central to this research. Chapter 3 provides an overview of the research methodologies employed to produce all aspects of this research. Results of original research from this thesis are then presented. Chapter 4 presents the results of a prospective assessment of IBD incidence rates and disease phenotypes in a geographically-defined Australian population over a 12 month period. An assessment of recent changes to local rates and patient phenotypes will also be made, and local results compared to international patient cohorts. Chapter 5 presents the prospective evaluation of IBD prevalence rates in the same region, providing a unique insight into the total burden of disease in this population. It also examines how many cases of IBD in the community are seen in the General Practice in isolation. Chapter 6 describes the establishment a local population-based IBD registry. The utility of the new pilot registry is then demonstrated by reviewing three-month clinical outcome data from a newly established inception cohort, focusing on factors that may assist clinicians in predicting which patients have the greatest risk of disease progression based on phenotypic features at the time of diagnosis. Finally, Chapter 7 concludes the thesis, providing a summary of the key results and findings from this research, a discussion of future challenges, and ideas for further research in this field.
CHAPTER 2.

BACKGROUND AND LITERATURE REVIEW

This chapter will serve as a general background introducing the major concepts related to the study of IBD. It provides a summary of our current knowledge, and provides the context in which this current research project has been developed. The bulk of the chapter focuses on areas of IBD most relevant to this research, in particular clinical epidemiology, incidence and prevalence calculations, and disease registry formation. However, a brief general overview of IBD covering important aspects of IBD definitions, pathogenesis, investigation and management, will also be described.

2.1 INFLAMMATORY BOWEL DISEASES

The two principal inflammatory bowel diseases are Crohn’s disease (CD) and ulcerative colitis (UC). A third, smaller group of patients with IBD do not meet strict diagnostic criteria for CD or UC, and are labelled as IBD unspecified (IBDU). In general terms, these conditions are chronic, idiopathic, inflammatory conditions that have their primary effects within the human gastrointestinal (GI) tract. They may also have potentially serious manifestations outside of the gut, including the skin, joints, liver and eyes. They are considered life-long conditions, and commonly have their onset in late adolescence or early adult years. A diagnosis of IBD can have a significant impact on physical functioning and quality of life, and lead to high personal and societal healthcare-related costs. The patterns and characteristics of disease vary between CD, UC and IBDU, and will be discussed below.

2.1.1 Crohn’s Disease

History

In 1913 the first reports of unexplained chronic inflammation of the GI tract were published (Dalziel, 1913). It was a further 19 years before the clinicians Crohn, Ginsberg and Oppenheimer defined a distinct clinical disease that was eventually labelled Crohn’s disease (Crohn et al., 1932). Subsequently, in 1954, a larger series of case observations from the Mayo clinic was published in the journal Gastroenterology, which provided some of the first information on clinical and pathological profiles of the disease (Van Patter et al., 1954).

Since these early landmark descriptions, our knowledge of CD has progressed immeasurably. As will be discussed in subsequent sections, one of the most striking observations made over the last 50-60 years relates specifically to features of disease epidemiology. This includes the observation of a significant rise in disease incidence over this time, in addition to unexplained geographical variations in IBD incidence, prevalence and behaviour. These observations have relied on the development of
high quality epidemiological research, highlighting the significance of this current population-based research project.

Pathology and Endoscopy

CD is characterised by chronic inflammation that can occur anywhere in the gastrointestinal tract, from the lips to the anal canal. CD is associated with full thickness, or trans-mural, intestinal inflammation (Thoreson and Cullen, 2007). Serious complications from this process include strictures resulting in intestinal obstruction, abscesses, and fistula formation. These fistulae most commonly occur between loops of bowel (entero-enteric fistula) or between the anorectum and the perineal skin (perianal fistula), but may occur between the bowel and any neighbouring organ or structure (Bernstein et al., 2010a).

Macroscopically, the endoscopic appearance of CD is one of patchy mucosal inflammation and discrete areas of ulceration, often described as “cobble-stone” in appearance. Although any part of the GI tract may be affected, CD is most commonly found to affect the terminal ileum and colon (Bernstein et al., 2010a). Microscopic features of active CD include a heavy inflammatory cell infiltration, composed mainly of plasma cells and lymphocytes, in addition to chronic structural or architectural distortion. Although not universally seen, the presence of organised, non-caseating granuloma composed largely of epithelioid histiocytes, are recognised as a pathognomonic hallmark of CD (Lichtenstein et al., 2009).

Clinical Features

Apart from the complications of CD described above, the presence of intestinal inflammation alone can produce a number of symptoms. These include abdominal pain, diarrhoea, faecal urgency, intestinal bleeding and weight loss (Stange et al., 2005). These distressing symptoms significantly impact on patient’s quality of life, influencing domains such as functional capacity, employment opportunity and emotional state (Andrews et al., 2010, Clearfield, 2008). Patients generally require a period of intensive medical intervention in the early stages to achieve disease remission. Population studies suggest that without maintenance therapy, up to 90% of patients will experience relapse of their condition at some stage, making complications and the need for surgical intervention more likely (Loftus et al., 2002). Disease phenotype, behaviour and evolution will be discussed in more detail later in this chapter.

As well as the intestinal-based disease processes described so far, CD can be associated with distressing extra-intestinal manifestations in up to 25% of cases (Bernstein et al., 2010a). Joint symptoms are common, with a reported prevalence ranging from 7 – 25% (Danese et al., 2005). Joint involvement can be peripheral or axial, and may antedate the diagnosis of IBD by several years (Peyrin-Biroulet et al., 2011b). Skin changes include pyoderma gangrenosum and erythema
nodosum. Ocular involvement can include iritis, uveitis and episcleritis. Conditions including osteoporosis, avascular necrosis, venous and arterial thromboembolism are all more common in patients with CD compared with the general population, relating both to the disease and associated therapy, including the use of corticosteroids (Danese et al., 2005). Liver associations include primary sclerosing cholangitis (PSC) with the risk of developing cirrhosis (Lichtenstein et al., 2009). Non-alcoholic fatty liver disease (NAFLD) is also more frequently seen in IBD patients when compared to the general population (Bernstein et al., 2010a). Gallstones and renal calculi occur more commonly in CD patients than the general population. Finally, mood disorders including anxiety and depression are significantly more common in IBD, with psychological manifestations seen in over 50% of CD patients (van Langenberg et al., 2008).

2.1.2 Ulcerative colitis

Pathology and Endoscopy

The key feature distinguishing UC from CD is that UC only affects the colon. Although mild inflammation can occasionally be seen in the very distal small bowel at endoscopy, this local change is thought to represent “backwash” from the inflamed colon rather than primary small bowel involvement (Meier and Sturm, 2011).

Another difference between UC and CD relates to both the macroscopic and microscopic appearance of the gut. While CD inflammation is generally discrete, patchy and characteristically deep, the appearance with UC is of continuous circumferential inflammation and superficial ulceration. Microscopically the inflammation in UC is also limited to the mucosa or sub-mucosal layers only (Thoreson and Cullen, 2007).

A third characteristic that can be used to separate the two conditions relates to the observed intestinal complications associated with each disease. As described, CD has been associated with intestinal perforation, fistulae, collections and strictures, but these features are less commonly associated with UC. The main serious intestinal complication of UC relates to severe colonic inflammation leading to toxic dilatation, with a risk of colonic perforation, significant morbidity and even mortality (Thoreson and Cullen, 2007). Higher rates of colorectal cancer (CRC) have been described in UC cohorts compared to CD cohorts, particularly relating to the length and duration of chronic inflammation (Lakatos and Lakatos, 2008)(Bergeron et al., 2010). As a consequence of this risk, colonoscopic surveillance of the colon for neoplasia during the long-term care of these patients is important (Carter et al., 2004).
Clinical Features

A review of previous large-scale population based cohorts has revealed the age of onset is often different between CD and UC. In general, UC appears 5-10 years later than CD. Some observational studies have suggested a slight male predominance in UC (Engal and Neurath, 2010). These epidemiological factors have only become apparent through the long-term follow-up of population-based IBD cohorts, highlighting the importance of this form of epidemiological research.

In most cases of UC, the length of colon involved and the intensity of the inflammation can predict the severity of symptoms. Common symptoms include abdominal discomfort, altered bowel function and the passage of blood per rectum. Faecal urgency and tenesmus secondary to rectal inflammation can be particularly distressing (Thoreson and Cullen, 2007).

Like CD, UC can also be associated with extra-intestinal features, including many of those listed previously for CD. There are some, however, that are more closely associated with UC. In addition to general arthropathy, specific HLA-B27 associated spondylitis is more commonly observed in UC. This can be a significant clinical disorder independent of gut symptoms, resulting in major joint inflammation, destruction and deformity, and is associated with high levels of disability. In addition, patients with UC who are HLA-B27 positive have higher rates of ocular complications including uveitis (Danese et al., 2005). In addition, pyoderma gangrenosum is more strongly associated with UC than CD (Thoreson and Cullen, 2007). Despite the differences described above, on occasion it may be difficult to differentiate UC from CD. Table 2.1 provides a comparison of the main features that differ between the two conditions and assist clinicians in accurate diagnosis.

Table 2-1 Comparison of UC and Crohn’s disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Colon only</td>
<td>From mouth to anus</td>
</tr>
<tr>
<td>Macroscopic description</td>
<td>Continuous ulceration and friability</td>
<td>Patchy ulceration and inflammation Skip lesions/cobble stoning</td>
</tr>
<tr>
<td>Microscopic features</td>
<td>Mucosa/Submucosal crypt abscesses, superficial ulcers</td>
<td>Transmural changes, aphthoid ulcers, granuloma</td>
</tr>
<tr>
<td>Usual Symptoms</td>
<td>Rectal bleeding, diarrhoea, abdominal pain</td>
<td>Abdominal pain, diarrhoea, wt loss, bleeding</td>
</tr>
<tr>
<td>Typical age at onset</td>
<td>35-45 years</td>
<td>30-40 years</td>
</tr>
<tr>
<td>Intestinal complications</td>
<td>Toxic dilatation, cancer development</td>
<td>Fistulae, abscesses, perforation, stricture formation</td>
</tr>
<tr>
<td>Serology</td>
<td>+ve ANCA*</td>
<td>+ve ASCA#</td>
</tr>
</tbody>
</table>

*ANCA – anti-neutrophil cytoplasmic antibody.
#ASCA – anti-Saccharomyces cerevisiae antibody.
2.1.3 IBD Unspecified (IBDU)

In a minority of cases of IBD no clear distinction between CD and UC can be made despite careful consideration of the clinical, radiological, endoscopic, and pathological features described previously. A label of inflammatory bowel disease unspecified (IBDU) is applied to this small patient group. IBDU had previously been referred to as Indeterminate Colitis (IC) or IBD unclassified, and is thought to account for approximately 5% of patients with IBD (Carter et al., 2004).

Patients with IBDU may have a combination of features of CD and UC at diagnosis, although a more definable disease phenotype often becomes apparent after a period of observation. A recent review of population-based follow-up studies including IBDU patients revealed that either CD or UC phenotypes eventually emerged in up to 80% of cases (Meucci, 2008).

A number of features may guide a clinician as to which phenotype is likely to evolve over time in cases of IBDU. Differences in the response to various therapies may predict the true underlying phenotype, and the presence of specific antibodies may further assist in some cases (Bernstein et al., 2010a). Anti-Saccharomyces cerevisiae antibodies (ASCA) are more strongly associated with CD, while peri-nuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are more commonly positive in UC. In a prospective study of 97 IBDU patients from Europe, Joossens et al found that positive serology had a positive predictive value (PPV) for delineating true IBD phenotype of between 66-80% for ANCA and ASCA respectively (Joossens et al., 2002). Furthermore, the role of capsule endoscopy in evaluation of IBDU patients is evolving, with the presence of typical small bowel ulceration suggesting a CD phenotype (Meucci, 2008).

It is possible that IBDU has been under recognised in historical cohort studies. Many cases of colitis were traditionally labelled as UC if no clear features of CD were present, however a more accurate diagnosis of IBDU might have applied. This has particular significance with regard to reviewing historical IBD incidence data, with a possible over-diagnosis of UC in these cohorts in patients who would currently be labelled IBDU (Henderson et al., 2011).

2.1.4 Aetiology and Pathogenesis: Established Influences

Although the immune mediated changes characteristic of IBD are well described, the underlying trigger responsible for initiating these changes remains unknown. It is currently accepted that IBD arises from a complex interplay between many factors. It is thought to occur as a result of the way a genetically susceptible individual interacts with particular environmental and gut microbial influences. The presence of certain gut microbiota appears to be crucial in activating and perpetuating the inflammatory process observed in IBD. For example, animal models demonstrate that IBD fails to develop in mice which are kept germ free from birth (Veltkamp et al., 2001). The
specifics of familial, genetic, microbial and environmental influences, and the way in which they are all thought to interact, are discussed in the following sections.

**Genetics**

There is strong evidence supporting a key role of patient genetic factors in IBD development. This includes the observation of clustering of cases within family groups, in addition to the concordance of IBD in twin studies. Many of the genes linked to IBD influence the host innate immune system and the way in which individuals interact with resident intestinal flora.

Observations over many years have suggested a tendency for IBD to cluster within families. In 1991 a landmark paper from Scandinavia assessed the familial clustering of IBD in Copenhagen County (Orholm et al., 1991). As compared to the general population, individuals who had a first degree relative with IBD had a 10-fold increase risk of developing IBD themselves. In another study Peeters et al observed a strong familial association for CD, particularly relating to age of onset and disease location (Peeters et al., 1996). A French study from the same time observed that the greater number of relatives an individual had with IBD, the higher the risk of subsequently developing IBD was (Colombel et al., 1996). Subsequently, it is now accepted that the greatest independent risk factor for developing IBD is having an affected family member with the condition (Russel and Satsangi, 2008).

Twin studies have allowed further quantification of genetic risk. The observed concordance rates for IBD in monozygotic twin studies has ranged from 20-50 % (Halfvarson, 2011, Orholm et al., 2000). The association is stronger for CD than UC (Halme et al., 2006). A recent paper from 2011 identified over 264 British twin pairs with at least one twin having IBD (Ng et al., 2011). In 28 of these twin pairs, both twins had IBD (concordant for disease). Interestingly this concordance occurred in both monozygotic and dizygotic twin pairs. An additional observation from this study was that phenotypic expression did vary in some concordant twin pairs, with some twins both having CD, some both having UC, and in some cases one twin having UC while the other had CD. Some consistencies in disease features were noted when both twins had the same form of IBD, with good correlation observed in age of disease onset and disease location. However, this association was again stronger for CD than for UC. In purely genetically driven disorders, disease concordance between monozygotic twins should be 100%. Twin data thus provides evidence that although genetics are important in IBD onset and disease behaviour, they are not the only factor to consider.

With regard to genetic risk, it is clear that IBD is a complex polygenic disease, with multiple genetic mutations contributing to IBD susceptibility to varying degrees. Recent advances in the field of genome wide association studies (GWAS) have allowed researchers to rapidly identify a large number of new susceptibility loci, which will likely account for a higher degree of observed disease
burden. Functional studies suggest many of the genes involved control immune regulation and the host's response to pathogenic stimulation.

Hugot and colleagues reported the first genome wide association study in CD in 1996 (Hugot et al., 1996). NOD 2/CARD 15 was then established as the first true susceptibility gene for CD five years later, with subsequent functional studies revealing that this gene is in fact involved in bacterial recognition and gut immune response mediation (Gaya et al., 2006). Since then, subsequent studies have uncovered a host of other disease susceptibility loci, loosely termed IBD 1-9. Whereas some loci appear specific to CD (IBD1 on 16q-OMIM 266600) or to UC (IBD2 12q-OMIM 601458), others seem to confer susceptibility to IBD in general (IBD3 6p-OMIM 604519). These observations reinforce the notion that these disorders are truly polygenic (Gaya et al., 2006). A recent meta-analysis of six CD genome wide association studies examined over 6000 cases and 14000 controls, and revealed a further 30 new potential susceptibility loci, bringing the total number of potential functionally significant candidate genes to over 70 (Franke et al., 2010).

Functional research has revealed that these genes play central roles in the innate immune system, specifically in the maintenance of the intestinal barrier, the transport of gut derived toxins, and the sensing of intestinal microbes (Pena, 2008). A recent paper from Southeast Asia examined race specific genetic influences and functional consequences. In this paper, particular IL23R polymorphisms seem to be protective against CD development in Western populations, but not in the Japanese population. Conversely, TNF SF 15 gene polymorphisms confers CD risk in both Japanese and Western populations (Leong et al., 2010).

Well designed, longitudinal, genetic/phenotypic linkage studies across a range of geographical locations will remain central to progressing our understanding of the pathogenesis of IBD, particularly with respect to the complexities of genetic and environmental interactions on disease phenotype and progression. Even in an era of technologically advanced genomic-based research, robust population-based cohorts and longitudinal epidemiological observational studies are still required.

**Microbial**

As previously discussed, the concept that IBD is not exclusively a genetic condition is now well established. Clinical observations and animal studies suggest intestinal flora play a key role in activating and perpetuating the intestinal inflammation characteristic to IBD. For example, genetically susceptible mice raised in a sterile environment do not develop intestinal inflammation (Dianda. et al., 1997). Previous microbial-based hypotheses on IBD pathogenesis have ranged from a single causative pathogen through to imbalances between protective and pathogenic naturally occurring enteric microbiota.
The theory of a single pathogenic organism causing IBD appears unlikely. However, this concept has been the subject of speculation from the time of the initial disease description in 1913 (Dalziel, 1913). For example, the granulomatous changes observed in human CD, and the similarities with the MAC-associated bovine granulomatous condition Johne’s disease, have long raised the suspicion of a Mycobacterium related organism being associated with IBD. However, while the literature surrounding CD and Mycobacterium avium paratuberculosis (MAP) in particular is conflicting and beyond the scope if this review, a definitive role of this organism appears unlikely.

The impact of Helicobacter-type organisms on IBD has also received significant research attention. This was initially based on animal models, and then subsequently on the observation of a severe non-IBD infective proctitis linked with this bacterium (Totten, 1985). More recently Zhang and colleagues found a 92% prevalence of Helicobacter organisms in children with IBD when compared to a background prevalence rate of 25% in healthy paediatric controls (Zhang, 2006). However, until more refined culture techniques and plausible pathogenic models are developed, a definitive association with Helicobacter is still lacking.

Several groups in North America and Europe have demonstrated an association with a novel adherent-invasive Escherichia coli species in relation to small bowel CD (Darfuille-Michaud et al., 2004). This species has also been demonstrated in animal models of colitis with granuloma formation, further supporting a possible link with CD (Simpson et al., 2006).

The evidence for familial clustering in IBD has already been presented. In addition to genetics, familial clustering may also be explained by exposure to shared infective agents. However, a very extensive study from 1993 of two French families with very high rates of IBD failed to find evidence of a single infective agent, examining a wide range of organisms including Campylobacter, Mycobacterium, Yersinia, Mycoplasma, coronavirus, Brucella, influenza, toroviruses and pestiviruses, with no dominant pathogen identified (Van Kruiningen, 1993). In addition to this study, the fact that there has never been a documented case of direct transmission of either CD or UC provides further evidence against the single infective pathogen argument.

There has been considerable recent interest in the study of the diversity of gut microbial content, termed the microbiota. Research has focused on the structure of the microbiota both in diseases such as IBD, and also in healthy controls. There is now evidence implicating commensal enteric bacteria in the pathogenesis of both CD and UC (Guarner, 2008). The human gut naturally has a rich supply of micro-organisms, crucial for normal health and digestion. These usually exist in a symbiotic relationship with the host (De Cruz et al., 2011). A reduction in the number of beneficial bacteria, and/or an excess of the harmful bacteria, has been theorised as being central to the pathogenesis of IBD. This imbalance may lead to changes in local bacterial metabolite levels, in turn affecting the
function of the gut epithelium by increasing mucosal permeability. This in turn leads to the activation of local innate and adaptive gut immune response, with chronic immune activity producing the inflammation that characterises IBD (Engal and Neurath, 2010).

Furthermore, there is evidence of an increase in the number of mucosal associated bacteria in IBD patients. Swidsinski and colleagues investigated the mucosal associated flora in over 300 IBD patients and 40 healthy controls using culture based techniques (Swidsinski et al., 2002). They found consistently increased levels of bacteria in colonoscopy biopsy samples in IBD patients when compared to health controls, with the number of bacteria rising in parallel to the underlying disease severity. Cultured species included Bacteroides, E.coli and Colinsella aerofaciens. Healthy gut mucosa is capable of preventing direct epithelial contact by luminal bacteria. It has been hypothesized that in the mucosal environment associated with IBD this ability is lost, with resultant increased host mucosal bacterial exposure and subsequent immune activation. However, Swidinski et al found that the actual concentrations of bacteria were highest in areas of non-inflamed mucosa, and not in areas of active inflammation. This raises the possibility that luminal bacteria themselves are not acting in a directly pathogenic way, and that the mucosal inflammation observed may be an epi-phenomenon to the bacterial presence through as yet unexplained mechanisms.

The role of fungi, viruses and helminths in IBD has also been extensively reviewed in the literature. The association between the presence of serum anti-\textit{Saccharomyces Cerevisiae} antibodies (ASCA) and CD has long been recognised. In addition to the non-pathogenic yeast \textit{Saccharomyces Cerevisiae}, \textit{Candida albicans} can also express the antigen responsible for ASCA production. It is also clear that candida make up part of the normal intestinal flora (Standaert-Vitse et al., 2006). The relationship between the presence of this fungus, the production of the ASCA antibodies and disease pathogenesis is still an area of evolving research.

Several viruses, including cytomegalovirus, parvo B19, norovirus and Epstein-Barr virus have all been implicated as agents responsible for changes in IBD activity. The role of the paramyxoviruses, in particular measles, has been extensively debated in the medical literature. In the decade after World War II, population studies revealed several measles outbreaks in Sweden that were subsequently linked to increased rates of CD (Ekbom et al., 1994). The same authors went on to suggest a possible risk of developing IBD from the administration of the live attenuated measles vaccination (Wakefield et al., 1998). However, subsequent studies did not support this finding, and in fact one US study actually showed a protective effect of measles vaccination in reducing rates of subsequent IBD (Davis et al., 2001). Overall, the available evidence does not support an association with either measles infection or vaccination, and IBD onset or disease activity (Loftus Jr, 2004).

The role of helminths in IBD, both with regards to aetiology and also their possible therapeutic application, has received increased attention recently. Host immune function profiling suggests that immune system exposure to intestinal worms can produce a beneficial host gut immune profile,
which is less likely to predispose to IBD onset. This concept is partly supported by considering the hygiene hypothesis. This hypothesis claims that with increasing urbanisation, humans are developing in more sterile environments (Green et al., 2006). This is associated with reduced environmental exposure to micro-organisms including helminths, influencing immune system development and subsequent susceptibility to autoimmune diseases. A critical review of the existing literature examining the significance of the hygiene hypothesis was published in 2008, supporting the association between decreased childhood microbial exposure and the risk of developing IBD (Koloski et al., 2008). The efficacy of manipulating the potential beneficial effect of luminal helminths for therapeutic applications has also been explored. One UC study looked at the efficacy of exposure to the pig hook worm Trichuris suis, showing a significant improvement in UC symptoms. They demonstrated reduced disease activity in 43.4% of the exposed group compared with 16.7% of a control arm (Summers et al., 2005). However, mechanistic, dose-finding and results from larger treatment cohorts are lacking, with further study required to clarify the true relationship between helminth infection and IBD pathogenesis.

Our understanding of the link between gut microbiota and IBD is rapidly evolving, particularly with the development of new laboratory techniques allowing accurate quantification and functional assessment of the gut flora. Specifically, advances in the field of metagenomics, allowing enhanced structural and functional characterization of gut microbiota, holds promise in unravelling the true role of microbes in IBD (De Cruz et al., 2011). It is important to note that this laboratory-based work will continue to be enhanced by the development of well designed population-based study cohorts, allowing ongoing microbial analysis in large populations of accurately characterised IBD patients.

Environmental and Other Influences

As demonstrated in the preceding sections, it is not possible to attribute all the risk for developing IBD to purely genetics or microbial influences alone. There is evidence to support the role of other factors in the pathogenesis of IBD.

Firstly, the disparity in disease onset and phenotype previously described between identical twins raised together suggests the influence of factors other than genetics and gut flora alone. Secondly, there is a disparity in IBD incidence and prevalence between developed or industrialised countries and underdeveloped regions, with further observations suggesting these differences reduce as a region becomes more developed. In addition, the rapid increase in disease incidence observed within some populations cannot be explained by changes in the local genetic pool alone (Ouyang et al., 2005). The study of IBD among immigrant populations provides strong evidence for the importance of local environmental factors influencing IBD pathogenesis (Williams, 2008). It has been observed that while the rates of IBD among new immigrants from areas of low to high IBD incidence (for example India, Asia to Europe or North America) remains low, rates of IBD in their offspring rises rapidly to match or even surpass the expected rates seen in the new region (Carr and Mayberry, 1999).
While it is clear that studying the role of environmental factors in disease pathogenesis is important, it is a difficult area of research with many potential biases impacting on the validity of results. Different study methodologies have been used in the past. A significant amount of information has been obtained from patients with an existing diagnosis of IBD, often made many years prior to study. The validity of these results, obtained through retrospective recall of environmental factors, needs to be interpreted with some caution. This data is subject to a significant element of recall bias. Despite this caveat, retrospective and some small prospective studies have identified a number of environmental factors that may be important in the understanding of IBD pathogenesis.

It has been proposed that development of IBD may be most strongly influenced by events that occur in early infancy and childhood. Factors that have been explored include mode of feeding, domestic circumstances, hygiene and peri-natal infections. Exposure to breast feeding may offer some protection against subsequent IBD development, although the evidence remains conflicting (Klement et al., 2004). On further review, the results of most of the older studies failed to reach statistical significance, and were all largely based on retrospective questionnaires (Loftus Jr, 2004). Koletzko et al published a small case control study in 1989 involving 145 families of children with IBD (Koletzko et al., 1989). They found that absence of breast feeding was associated with a subsequent elevated risk of developing IBD. A prospective nested case-control study observing two large birth cohorts in Europe previously demonstrated a non-statistical trend toward breast feeding protecting against the onset of CD, with an odds ratio (OR) of 0.4 (range 0.15-1.03) (Thompson et al., 2000). A more recent large population-based study undertaken through the Canterbury region in Southern NZ suggested that breast feeding reduced the risk of disease onset, for both CD (OR 0.55 [0.41-0.74]) and UC (OR 0.71 [0.52-0.96]) (Gearry et al., 2010). Furthermore, it appeared there was a clear duration-response relationship, with the protective association only observed for infants who were breast fed for more than 3 months. These observations may have a microbial basis, as breastfed infants have previously been observed to have higher levels of bifidobacteria and lower levels of anaerobic organisms in their faeces than their bottle-fed counterparts (Fanaro et al., 2003).

The components of diet present a significant antigenic burden to the gut mucosa, and impacts on both local and systemic immune responses. This suggests a possible pathogenic role for dietary components and conditions like IBD. A link between disease onset and diet could further explain some of the differences in IBD rates observed between various geographical regions, and also within different socioeconomic groups within the same region. This possible association has been recognised and studied for over 40 years. An early report from the BMJ in 1979 suggested a possible increase risk of CD onset with a diet high in refined sugar but low in fibre, raw fruit and vegetables (Thornton et al., 1979). Longitudinal studies have subsequently supported some of these links, particularly the association with diets high in processed carbohydrates predisposing to IBD onset. There is additional evidence suggesting that a diet high in refined sugar and low in vegetables, recognised as a “Western Diet”, may increase the risk of developing IBD. Adolescents who consume more than two takeaway meals per week show increased risk of developing CD (OR 2.09 [1.13-2.89])
One Swedish study also found the highest risk of IBD onset regarding diet related to an intake high in ‘fast food’, with a RR of 3.4 (CI 1.3-9.3) (Persson et al., 1992).

However, significant weaknesses exist with much of the evidence implicating diet in IBD. One factor that confounds the association between diet and IBD is that patients who begin to have symptoms prior to their diagnosis may vary their dietary intake to compensate for these symptoms, such as naturally reducing fibre in the diet and consuming more refined food groups. Secondly, the issue of recall bias in these patients is important to consider. This may be partially reduced by targeting patients with a very recent diagnosis of IBD, for instance within 12 months, when the recall is likely to be most accurate.

While many of the environmental factors associated with IBD are common to both CD and UC, smoking does not follow this pattern. Smoking in IBD has been extensively studied, and is closely linked with IBD risk, specific phenotypes and also disease course or behaviour. However these effects are different when comparing CD to UC. While the precise reason for this association is unknown, affects on colonic mucin production, mucosal barrier dysfunction and the immune system have all been postulated (Thoreson and Cullen, 2007, Ali and Tamboli, 2008). In UC, the risk of new onset disease is reduced in current smokers. Ex-smokers have a higher risk of UC onset, suggesting some protective effect of smoking against UC developing. This is further supported by observation of a higher frequency of clinical disease flares in smokers with pre-existing UC who quit smoking. Conversely, smoking is a risk factor for CD (García Rodríguez et al., 2005). CD patients who continue smoking have a more aggressive disease course and are prone to earlier and more severe post-operative recurrence (Caprilli et al., 2006). Recent work from New Zealand has revealed an increased risk of developing CD in children whose mothers smoked during their pregnancy (Gearry et al., 2010). However, the precise relationship between smoking and IBD remains to be fully determined, with some conflicting results from large population-wide observations. Smoking rates in Asia and Africa are among the highest in the world (up to 65% of adult males), yet these areas have traditionally had very low rates of IBD.

Previous appendicectomy is another factor that seems to influence the onset of IBD, showing a disparate effect on CD compared with UC (Gearry et al., 2010). While appendicectomy appears to protect against UC onset, this has not been observed for CD (Thompson et al., 2000). The observed differences in IBD onset, and possibly behaviour, are postulated to relate to the immune function of the appendix, however the specific details and implications of this are not yet fully understood.

There has been interest in the potential role of stress in IBD pathogenesis, both as an aetiological factor and as a factor in triggering flares of disease. However, the evidence remains inconclusive. Stress is subjective and difficult to reliably quantify for research purposes. Retrospective questionnaires with recall of stressful events in relation to disease activity are prone to recall bias (Andrews and Holtmann, 2011). Bernstein et al recently published more methodologically sound,
prospective data regarding the impact of stress on IBD, from a large population-based registry (Bernstein et al., 2010b). Patients completed a questionnaire every three months for a year, with validated assessment of stress levels and disease activity. The prospective use of this population-based registry overcame many of the weaknesses seen in the older retrospective recall studies. The authors were also able to assess several other potential influences on disease activity including non-steroidal anti-inflammatory drug (NSAID) use, antibiotics and infections. While no clear association between NSAID use, antibiotics and infections and changes in disease activity was demonstrated, the authors did find a correlation between increased stress levels and increasing perception of IBD related symptoms. Unfortunately, the score used to assess disease activity may have also reflected irritable bowel syndrome (IBS) type symptoms. No objective disease activity markers were used in this study. It could thus be concluded that stress plays a role in IBD symptom perception, however strong evidence linking stress and disease onset or objectively defined increased disease activity, is lacking.

The lifestyle and environmental factors described above provide potential novel insights into IBD pathogenesis. Research in this area continues to evolve. Although historical data is largely retrospective, future research will need to focus on prospective study design using validated, large-scale, population-based cohorts, identified early in their disease course.

### 2.2 CLINICAL AND PRACTICAL ISSUES IN IBD

Careful consideration of the clinical and practical issues related to IBD is crucial when planning the design and methodology for population-based epidemiology research. An appreciation of these factors is key to the ultimate validity of all results generated from such research, including disease incidence and prevalence rates, and disease behaviour observations.

#### 2.2.1 Differential Diagnosis

Careful consideration for the broad differential diagnosis for IBD remains important when considering IBD research. No single diagnostic test is currently available to confirm the diagnosis of IBD. The diagnosis therefore remains based on a composite of characteristics including history, examination, imaging, histology and possibly serological findings. Through this process, the differential diagnoses listed in this section can generally be excluded, although this may prove difficult in some cases. Current best practice diagnostic standards for CD and UC are discussed in subsequent sections. These are very important to consider when designing new population-based epidemiological studies and when reviewing the results of historical research, as how a diagnosis of IBD is made has significant impact on case ascertainment and diagnostic accuracy.

Diarrhoea secondary to intestinal inflammation is a common clinical problem in the community, with the vast majority of cases being mild and related to acute, self-limiting infective agents. However,
mucosal inflammation may also be a non-specific response by the gastrointestinal tract to a range of other insults. While assigning a diagnosis of acute infective gastroenteritis may be straightforward based upon a positive stool microscopy and culture result in a patient with symptom duration of less than two weeks, consideration of a differential diagnosis is important for patients where an infective cause cannot be established. Tables 2.2, 2.3 and 2.4 outline some of the possible differential diagnoses to consider, broken down by location of intestinal inflammation (Adapted from (Sands, 2004) and (Nikolaus and Schreiber, 2007)).

### Table 2-2 Differential Diagnosis of Ileitis.

<table>
<thead>
<tr>
<th>Infection</th>
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<tbody>
<tr>
<td><em>Yersinia enterocolitica, Yersinia pseudotuberculosis</em></td>
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<tr>
<td><em>Mycobacterium tuberculosis, Mycobacterium avium–intracellulare complex</em></td>
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<tr>
<td>Typhitis</td>
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<tr>
<td><em>Histoplasma capsulatum</em></td>
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<td><em>Salmonella</em></td>
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<tr>
<td>Cryptococcosis</td>
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<tr>
<td>Anisakiasis</td>
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<tr>
<td><em>Actinomyces israelii</em></td>
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<tr>
<td><strong>Inflammation</strong></td>
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<tr>
<td>Appendicitis</td>
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<tr>
<td>Appendiceal abscess</td>
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<tr>
<td>Caecal diverticulitis</td>
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<tr>
<td><strong>Gynaecologic</strong></td>
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<tr>
<td>Pelvic inflammatory disease</td>
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<tr>
<td>Tubo-ovarian abscess</td>
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<tr>
<td>Ovarian cyst or tumour</td>
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<tr>
<td>Endometriosis</td>
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<tr>
<td>Ovarian torsion</td>
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<tr>
<td>Ectopic pregnancy</td>
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<tr>
<td><strong>Neoplasm</strong></td>
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<tr>
<td>Caecal or small bowel (ileal) adenocarcinoma</td>
</tr>
<tr>
<td>Lymphoma</td>
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<tr>
<td>Lymphosarcoma</td>
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<tr>
<td>Carcinoid tumour</td>
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<tr>
<td>Metastatic cancer</td>
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<tr>
<td><strong>Drug-related</strong></td>
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<tr>
<td>Non-steroidal anti-inflammatory drug-related ulcer or stricture</td>
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<tr>
<td>Ischemic: oral contraceptives, ergotamine, digoxin, diuretics, anti-hypertensives</td>
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<tr>
<td><strong>Vascular</strong></td>
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<tr>
<td>Atherosclerosis associated ischemia</td>
</tr>
<tr>
<td>Vasculitides: polyarteritis nodosa, Churg–Strauss syndrome, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell arteritis, rheumatoid arthritis vasculitis, thromboangiitis obliterans</td>
</tr>
<tr>
<td>Henoch-Schonlein purpura</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Behcet’s syndrome</td>
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<tr>
<td><strong>Infiltrative</strong></td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Lymphoid nodular hyperplasia (normal or suggestive of IgG deficiency)</td>
</tr>
<tr>
<td><strong>Torsion of the appendiceal epiploca</strong></td>
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<tr>
<td>Ileitis associated with spondyloarthropathy</td>
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<tr>
<td>Backwash ileitis arising in ulcerative colitis</td>
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<tr>
<td>Radiation enteritis</td>
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</tbody>
</table>
Table 2-3 Differential Diagnosis of Proctitis.

Rectal Prolapse
Solitary rectal ulcer syndrome
Trauma
Chemical or radiation injury
Infection (including sexually transmitted disease)
  Herpes simplex type II, CMV
  Neisseria gonorrhoeae
  Syphilis (Treponema pallidum)
  Lymphogranuloma venereum
  Chlamydia trachomatis
  Whipworm infestation
Ulcereative proctitis
Crohn’s proctitis

Table 2-4 Differential Diagnosis of Colitis.

Ulcerative colitis
Crohn’s colitis
Indeterminate colitis
Acute self-limited colitis
Segmental colitis associated with diverticular disease
Diverticulitis
Infections
  Cytomegalovirus
  Shigella
  Campylobacter
  Clostridium difficile
  Salmonella
  Aeromonas pleisioides
  Amaebiasis
  Enterohemorrhagic E. coli (EHEC)
  Mycobacterium tuberculosis
  Yersinia enterocolitica
  Schistosomiasis
  Strongyloides
  Ischemic colitis
  Behcet’s disease
  Microscopic colitis
  Collagenous colitis
  Lymphocytic colitis
  Radiation colitis
  Diversion colitis
  Chronic granulomatous disease
  Graft-vs.-host disease
  Gastrointestinal sarcoidosis
  Eosinophilic gastroenteritis
  Drug-related (NSAIDs, gold, penicillamine)
In routine clinical practice, an infective cause of gastrointestinal symptoms is most common, and should be first excluded by detailed stool microscopy, assessment of bacterial toxins, and stool culture. After infective causes, the next broad category of conditions which produce GI inflammatory changes are gastrointestinal ischaemia, changes from the direct effect of ionising radiation, and medication use (in particular the use or abuse of non-steroidal anti-inflammatory drugs). Microscopic colitis can also mimic IBD symptoms and is an important differential diagnosis to exclude (Lichtenstein et al., 2009). In Western society, functional bowel diseases, such as irritable bowel syndrome (IBS), remain an important and common differential to consider, particularly when no objective evidence of intestinal inflammation is found. Differences exist between adult and paediatric patients when considering these differentials, as many conditions listed are uncommon in young patients.

2.2.2 Diagnostic and Investigation Modalities

A diagnosis of IBD is made by considering the results of a number of different investigations in the context of an individual’s clinical history. There is no single diagnostic test. The tools available to investigate possible IBD patients have evolved remarkably since the earliest recognition of IBD. These are outlined in the following section.

A brief history of diagnostic evaluation

The earliest reports of IBD, including those by the Scottish surgeon Dalzeil in 1913, were all largely based on the examination of surgical specimens. The advent of endoscopy, firstly with rigid equipment and then subsequently with development of safer and more clinically acceptable flexible fibre-optic endoscopes, rapidly progressed the ability to interrogate the bowel in search of disease. Imaging of body systems first began in the early 20th century, firstly with plain x-ray imaging, and has more recently seen a rapid evolution through computer tomography (CT), ultrasound (U/S) and most recently magnetic resonance imaging (MRI) and positron electron tomography (PET). The field of IBD diagnostics that has been further advanced most recently are the areas of genetics and serological markers. While these new technologies offer unique insights into disease pathogenesis, they have yet to become part of the standard diagnostic workup.

A proposed minimum diagnostic evaluation in suspected IBD published in 2010 by the World Gastroenterology Organization (Bernstein et al., 2010a) includes;

1) Comprehensive history
2) Physical examination
3) Stool analysis to exclude infection
4) Full blood examination (FBE), albumin, ferritin, C-reactive protein (CRP)
5) Human Immunodeficiency Virus (HIV)/Tuberculosis (Tb) testing if from high risk population
Clinical history and examination in IBD

The heterogeneity of clinical manifestations, the potential insidious non-specific onset of symptoms, the overlapping features of alternative inflammatory conditions, and occasionally the presentation of IBD in the absence of gut specific symptoms, all make the diagnosis of IBD a significant challenge for the clinician. The symptom profile and examination findings are both dependent on many factors. These include individual patient factors (past history, social circumstances, cultural considerations, etc), disease location, and also disease severity. A thorough assessment of these factors is central to both establishing a diagnosis of IBD from the differentials discussed in the preceding sections, and also in differentiating CD from UC.

Classically, diarrhoea (defined as increased stool frequency and/or reduced stool consistency) is the most common symptom in IBD presentations (Engal and Neurath, 2010). A careful social history suggesting risk of exposure to infective agents is important to consider. In general, acute onset diarrhoea of less than 2 weeks duration is usually infective in origin. However, if symptoms are present for more that 2-4 weeks IBD becomes an important consideration as infective causes are less likely to persist for this length of time (Sands, 2004). However, diarrhoea is not a universal symptom in IBD. Approximately 5 – 10% of patients with purely rectal inflammation may paradoxically present with constipation, often associated with tenesmus (the feeling of constantly needing to pass stools associated with pain and incomplete evacuation) (Sands, 2004).

Abdominal pain is the second most common presenting feature of IBD (Sands, 2004). UC is more likely to cause left iliac fossa discomfort and stool urgency, while CD with terminal ileal inflammation can present with right iliac fossa pain and tenderness. Colonic inflammation may also result in significant PR bleeding, and is more commonly associated with UC (Lichtenstein et al., 2009). Alternatively, a history of peri-anal disease, such as fistula, abscess or recurrent fissures, would favour a diagnosis of CD.

It is accepted that IBD is a systemic disease. Although the focus of disease burden is primarily in the GI tract, IBD can manifest in other organ systems. A significant proportion of IBD patients suffer from extra-intestinal manifestations (EIMs). Of these, a quarter will have more than one EIM. The onset
of EIM’s may predate a diagnosis of IBD (Bernstein et al., 2010a). Table 2.5 describes some of the possible EIM’s observed in IBD (adapted from (Danese et al., 2005)).

Table 2-5 Extra-intestinal manifestations of IBD (prevalence estimates in brackets).

<table>
<thead>
<tr>
<th>Cutaneous (10-20%)</th>
<th>Urinary (&lt;10%)</th>
<th>Rare Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema nodosum (3-8%)</td>
<td>Nephrolithiasis (2-6%, more common in CD)</td>
<td>Chronic recurrent multifocal osteomyelitis</td>
</tr>
<tr>
<td>Pyoderma gangrenosum (1-2%)</td>
<td>Renal amyloid (1%, more common in terminal ileal CD)</td>
<td>Myositis</td>
</tr>
<tr>
<td>Rheumatologic (7-25%)</td>
<td></td>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td></td>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scleritis, Episkleritis, scleroconjunctivitis</td>
<td></td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Uveitis, Iritis</td>
<td></td>
<td>Pleuropericarditis</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td>Lymphocytic encephalomyeloneuritis</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis (2-7%, more common in UC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease (NAFLD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis (NASH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption/Inflammation related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenia (40-50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (2-30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe Deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B12 Deficiency (more common in CD affecting stomach and terminal ileum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercoagulability (venous and arterial) with thromboembolism (1-6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.6 outlines some clinical signs associated with IBD (adapted from (Sands, 2004)). Physical findings may be variable and non-specific, both with respect to differentiating IBD from other differential diagnoses, and also differentiating UC from CD.
### Table 2-6 Physical findings or signs observed in IBD.

**Fever** – not specific for IBD, but when seen is more associated with CD than UC

**Clubbing** – more in CD than UC, indicating chronic inflammation

**Growth failure** – particularly in paediatric onset IBD

**Anaemia** – seen in both CD (Fe and B12 deficiency related plus anaemia of chronic disease) and UC (Fe deficiency and anaemia of chronic disease)

**Ocular** – more common in CD

**Mucocutaneous findings**

- Mouth ulcers – non-specific and common in both UC and CD (but also in general population)
- Erythema nodosum – possibly more frequent in CD
- Pyoderma gangrenosum – possibly more frequent in UC

**Abdominal mass** – particularly in right iliac fossa region suggests CD related inflammatory mass or collection

**Peri-anal findings (skin tags, fistula, fissure)** – all more common in CD

**Anal stenosis** – suggests CD

### Endoscopic Assessment and Histology

The major procedure central to the diagnosis and monitoring of IBD remains conventional endoscopy. This allows both direct mucosal inspection and tissue biopsy for histopathology (Engal and Neurath, 2010). Endoscopic assessment plays a key role in defining IBD phenotype and distribution, in addition to guiding severity assessment and prognosis.

Colonoscopic features of UC include continuous superficial inflammation commencing in the rectum, with erythema, mucosal granularity, shallow ulcers, and contact friability commonly seen. Extensive regenerative hyperplasia can be associated with both CD and UC, however is more closely associated with UC (Engal and Neurath, 2010, Sands, 2004). CD is recognised as typically more patchy inflammation, classically described as a cobble-stone like appearance. The ulcers themselves are often more complex, deeper and stellate in macroscopic appearance (Sands, 2004). While the presence of minor terminal ileal inflammation may be a feature of the ‘backwash’ effect seen from the amount of colonic inflammation observed in extensive UC, active ileal inflammation is more strongly associated with a diagnosis of CD. The presence of aphthous or deeper ulcers in the TI strongly suggests CD. Furthermore, inflammation and ulceration in any other proximal part of the gastrointestinal tract would suggest CD as the most likely IBD phenotype.

Histopathological assessment remains crucial for IBD diagnosis, and can further assist in differentiating UC from CD. UC is characterised by the infiltration by neutrophils into submucosal crypts, cryptitis and crypt abscess formation with disturbed crypt architecture, and mucous
depletion in goblet cells. This latter feature is less commonly seen with CD. Microscopic features suggesting CD include heavier T cell and monocyte infiltrate, and the presence of granuloma. However, granuloma are only seen in 40-60% of CD resection specimens and even less frequently in biopsy samples. While granuloma have a high specificity for CD, they do lack sensitivity (Engal and Neurath, 2010). Another classical microscopic feature of CD that is best appreciated on resection specimens rather than biopsy samples is the trans-mural and possibly penetrating changes observed. A European Crohn’s and Colitis Organisation (ECCO) consensus from 2005 suggested that the microscopic diagnosis of CD is more certain if there are at least three of the above features present in the absence of granuloma, or one additional feature when granuloma are identified (Stange et al., 2005).

Imaging Modalities

Plain abdominal imaging has a low radiation exposure, and may still have a role in IBD diagnosis and management. While findings are not necessarily specific for IBD, it may demonstrate the extent of inflammation, to diagnose complications such as bowel perforation or intestinal obstruction, and remains a very useful tool in assessing risk of perforation with toxic dilatation in the setting of acute severe colitis, (Bernstein et al., 2010a). Furthermore, incidental findings of EIMs including renal tract stones or axial skeletal inflammatory changes (sacro-iliitis), may be seen (Stange et al., 2005).

The use of barium small bowel follow-through (SBFT) and double contrast barium enema (DCBE) have declined in recent years, however these techniques may still have a role in some situations. SBFT remains helpful in visualising the upper GIT through to the distal small bowel, while DCBE can be useful in reviewing colonic segments that are not able to be adequately visualised at colonoscopy due to either angulation or disease-related strictures (Bernstein et al., 2010a). The anatomy of fistulae can also be defined with both these techniques.

Cross sectional imaging (CT and MRI) are now generally the preferred imaging techniques, as they offer a number of advantages. Accurate assessment of luminal disease extent and activity, plus the detection of extra-intestinal complications, is possible. The role of both MRI and CT in IBD are rapidly evolving. Both techniques have been shown to accurately establish the presence and length of small and large bowel inflammation, and have good sensitivity and specificity in detecting complications of IBD including perforation, abscess formation, stenosis and bowel obstruction (Zalis and Singh, 2004). MRI offers a significant benefit over CT due to the absence of radiation. Radiation and subsequent cancer risk becomes is an important issue in IBD, particularly when considering the young age of these patients, and the need for repeat imaging throughout their disease course. An average CT enterography exposes the patient to around 8mSievert of radiation, over twice the usual background yearly radiation exposure (Allen et al., 2011). MRI is also superior in imaging the complex anatomy of the peri-anal region in patients with locally fistulising CD (Lichtenstein et al., 2009). Cost and access remain an issue in Australia for MRI, as there is no current government rebate for this indication. Another area of uncertainty relates to the specificity of these new
technologies, with uncertainty regarding the significance of minor and/or subtle findings seen within the small bowel on imaging.

Ultrasound (U/S) remains a technique that is utilised in investigating some patients with suspected IBD. The benefits of trans-abdominal U/S in IBD assessment include its non-invasive nature and the lack of radiation exposure. However, it is prone to considerable individual operator variation as well as difficulties in imaging segments of highly mobile and gas filled segments of small bowel. U/S remains to be extensively validated in IBD. Hollerbach et al prospectively assessed the ability of U/S to differentiate different inflammatory bowel conditions including appendicitis, diverticulitis and IBD. They found that while specific for detecting inflammation, the sensitivity of U/S in identifying CD was reduced to 84%, and 66% for UC, with better detection for changes in the terminal ileum and colon (Hollerbach et al., 1998). Similar studies in the post-operative setting have been done, with some promising results in detecting those at higher risk of recurrence seen (Dubinsky and Seidman, 2000). Experience with U/S in IBD comes largely from Europe, where the use of U/S forms part of normal gastroenterology training. This is not the case in Australia, with problems arising from inter-observer variability and reproducibility.

Emerging diagnostic modalities

A number of new techniques are under development in the field of IBD diagnosis. Although offering potential novel approaches to investigation, diagnosis and prognosis, they are yet to form part of the standard approach to investigating IBD.

Capsule Endoscopy

The use of the swallowed video capsule endoscope (VCE) has recently been assessed in the diagnostic evaluation of IBD (Lichtenstein et al., 2009). While generally well tolerated, a number of issues related to VCE have hindered its wide use in the work-up of suspected IBD. Firstly, there is a risk of capsule retention within the small bowel, particularly relevant in CD where pre-existing disease related strictures may occur. Secondly, the diagnostic accuracy and significance of small erosions and ulcers seen in the small bowel on VCE are yet to be fully understood (Lichtenstein et al., 2009). Until capsule findings are fully validated in IBD, there is a risk of over estimation of new cases due to the presence of minor small bowel changes, having potentially a significant impact on disease incidence and prevalence rates derived in future epidemiological studies. Finally, the lack of ability to obtain tissue samples and difficulties with clear colonic mucosal examination, further hinder the current application of VCE in IBD. Despite these limitations, VCE has been approved as part of the work-up for suspected IBD in the USA (Kane, 2008). This is not yet the case in Australia, with no access to government rebates for VCE for this specific indication alone.
Enteroscopy

The emerging endoscopic techniques of single or double balloon enteroscopy (SBE/DBE) have the potential to offer complete pan-endoscopy, with particularly good visualisation of small bowel mucosa (Ali and Tamboli, 2008). In addition, the techniques offer the advantages of allowing tissue sampling to occur, and also for the application of endoscopic therapy including the dilation of intestinal strictures commonly seen in CD. This may then avoid the need for more extensive intestinal surgery or resection in these patients. Limitations of this technology include access difficulties secondary to equipment and hospitalisation costs, and the high level of operator training required. The procedures are associated with risk, including complications such as perforation, and generally require general anaesthesia. The true diagnostic yield and benefit of SBE/DBE in the investigation of IBD has not yet been accurately determined.

Serology, Biomarkers and Genetics

The study of serological markers in IBD is evolving, although they are yet to find a role in routine clinical practice. ASCA and ANCA have been described in previous sections. Newer markers including Interleukin 6 (IL-6), antibodies against the outer membrane porin C of *E.coli* (anti-OmpC), antibodies against a *Pseudomonas fluorescens*-associated sequence I2 (anti-I2) and antibodies against the flagellin Cbir1 (anti-Cbir1), have all been evaluated more recently (Dubinsky and Seidman, 2000, Klebl et al., 2004, Ferrante et al., 2007), and are likely to play an important role in the future with regard to diagnosis and identification of high risk phenotypes.

Faecal markers such as lactoferrin and calprotectin appear to be sensitive in detecting active intestinal inflammation associated with IBD, and commercially available assays for these markers are now available (Dubinsky and Seidman, 2000). Calprotectin is increasingly used as a test to differentiate IBD symptoms from IBS and to predict the presence of persistent mucosal ulceration in patients who appear to be in clinical remission. Faecal calprotectin is an increasingly attractive and objective, non-invasive method of serial disease assessment and activity monitoring, and may be useful in following disease activity in IBD cohorts (Ali and Tamboli, 2008).

Genetic analysis, with particular reference to the technique of genome wide associated study (GWAS), has lead to the discovery of several genetic markers implicated in disease susceptibility, phenotype and in predicting clinical outcomes. However, these are yet to find a role in routine clinical care in IBD, with the role of these tests in diagnosis and predicting disease behaviour still evolving (Van Limbergen et al., 2007).

The fields of IBD genetics, serology and disease biomarkers are rapidly evolving. The future of IBD diagnostics will likely involve reviewing a combination of faecal and serum markers, in combination with a patient’s genetic profile, to aid in both diagnosis and prognosis. Ultimately, this will allow
personalised medicine, with tailoring of an individual therapeutic approach for each patient (Nikolaus and Schreiber, 2007). The continued establishment of accurately characterised IBD cohorts will be crucial for the future validation of these new IBD markers.

2.2.3 Diagnostic Criteria in IBD

No single diagnostic test is available for IBD. Accurate diagnosis currently relies on considering a composite of factors including history, examination, endoscopic evaluation, histopathology, and biochemical/imaging studies (Stange et al., 2005). Within this nebulous framework, there is considerable variability in the literature regarding the accurate diagnosis of new IBD cases. While further support in diagnosing IBD may be gained from reviewing serological and faecal biomarkers and identifying a compatible genetic profile as described previously, these techniques remain largely research tools, and yet don’t form part of the routine diagnostic criteria in current practice.

A number of challenges still exist with regard to establishing a diagnosis of IBD. The European Crohn’s and Colitis Organisation (ECCO) consensus statements on CD diagnosis reflect on some of these difficulties, with reference to the heterogeneous presentations, and also the variety of disease phenotypes observed (Stange et al., 2005, Van Assche et al., 2010). The chronic relapsing nature of IBD, in addition to the insidious onset of symptoms that is often observed, further complicates accurate diagnosis early in disease course. Finally, the broad range of differential diagnoses that may mimic IBD can confuse the diagnosis further.

When comparing the results of different epidemiological studies of IBD, it is crucial to consider the disease definitions and diagnostic pathways used to confirm IBD as this has a significant impact on the quality of the data presented. Below is a review of some of the diagnostic criteria that have previously been proposed.

EPICOM diagnostic criteria

The recently established Europe-wide IBD inception cohort, investigating the possible east-west-gradient in IBD and the relationship to Vitamin D, used the following diagnostic criteria based on previous Danish IBD epidemiological studies (Burisch et al., 2011).

EPICOM case inclusion;

Copenhagen Diagnostic Criteria (CD) (Munkholm, 1997) – at least two of the criteria present;

1. History of abdominal pain, weight loss and/or diarrhoea for more than three months
2. Characteristic endoscopic findings of ulceration (aphthous lesions, snail track ulceration) or cobble stoning or radiological features of stricture or cobble stoning
3. Histopathology consistent with CD (epithelioid granuloma of Langerhans type or transmural discontinuous focal or patchy inflammation)
4. Fistula and/or abscess in relation to affected bowel segments

Copenhagen Diagnostic Criteria (UC) (Langholz, 1999) – all three criteria present;

1. History of diarrhoea and/or rectal bleeding and pus for more than a week or repeated episodes
2. Characteristic endoscopic findings of continuous ulceration, vulnerability or granulated mucosa
3. Histopathology consistent with UC (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses)

Where intestinal inflammation with acute and chronic colitis is seen but with no pathognomonic histological signs of CD or consistent signs of UC, and where treatment is necessary, the diagnosis of indeterminate colitis (or IBDU) was made.

**European Crohn’s and Colitis Organisation (ECCO) Consensus statements**

ECCO have released two evidence-based consensus statements on CD diagnosis (Stange et al., 2005, Van Assche et al., 2010). The second edition was published in 2010, comprising a 20 page document covering all aspects of diagnosis, and reflecting on the clinical complexities involved in establishing a diagnosis of CD. With regard to history, a time frame of 6 weeks of symptoms was recommended, although the guideline also reflects on the fact that some patients may present more acutely than that, particularly those with terminal ileal disease. The need for focal and chronic inflammatory changes in biopsy samples was also emphasized. Unfortunately no clear diagnostic pathway or clear list of criteria was presented in either position statement, again reflecting on the difficulties and complexities in diagnosing CD.

**World Gastroenterology Organisation Practice Guidelines 2010**

The World Gastroenterology Organization, in recognising the unique and complex issues relating to accurate IBD diagnosis, published practice guidelines in 2010 (Bernstein et al., 2010a). While similar to the ECCO guidelines, the WGO statement suggests case confirmation 3-6 months from initial diagnosis to confirm that no alternative diagnosis has emerged. Unfortunately, no clear cut-off for symptom duration is made. While the WGO guideline describes the principal of the diagnosis of IBD
relying on a composite of clinical, endoscopic, radiologic and histological findings after the reasonable exclusion of alternate differential diagnoses (particularly infective processes) they are unable to present a set of simple, clear, and definitive diagnostic criteria.

**Diagnostic criteria used in other population-based research**

Researchers involved in a prospective population-based study from northern France, published in 1994, divided cases of CD and UC into ‘definite, probable and possible’ based on a composite of symptoms and investigation findings (Gower-Rousseau et al., 1994). The minimum length of symptoms prior to presentation was 6 weeks for most cases, however a definite diagnosis of CD was made if granuloma were seen in any case, irrespective of the length of clinical symptoms.

In the landmark paper from Canterbury, New Zealand, establishing IBD incidence and prevalence rates from 2003/05, Gearry et al used the following criteria for IBD diagnosis (Gearry et al., 2006);

1. Typical clinical features including abdominal pain, weight loss, and diarrhoea for greater than 4 weeks,
2. Macroscopic features at operation of endoscopy,
3. Radiological evidence of small or large bowel inflammation, stenosis or fistulae,
4. Histological evidence of transmural inflammation or granuloma.

Effort was made to also exclude infection, ischaemia, drug effects or malignancy. Continuous inflammation from the rectum without features of CD was labelled UC, with uncertain cases identified at indeterminate or IBDU.

More recently, Wilson et al published prospective IBD incidence rates estimations in the Geelong Region of Victoria, Australia (Wilson et al., 2010). Clinically-based criteria were also used, and all cases were reviewed three months from initial identification before they were included as a true incident case. A summary of the criteria used are presented below.

**Inclusion criteria;**

1. Consistent clinical features including abdominal pain, diarrhoea, bleeding or weight loss for > 4 weeks,
2. Endoscopic requirements included ulceration of inflammation consistent with CD of UC,
3. Radiological evidence of small or large bowel inflammation,
4. Histology consistent with IBD, with findings including inflammation and granuloma (CD),
5. Rigorous efforts to exclude differentials including infections, ischaemia, non-steroidal anti-
   inflammatory drug ulceration and radiation through consideration of history, medication use
   and stool examination,
6. Clinical notes of cases individually reviewed, initially at time of diagnosis and again three to
   six months later, to ensure accurate classification of cases.

These rigorous criteria reflect that the emphasis of this Australian study was on specificity over
sensitivity, reducing the chance of overestimation of incidence rates.

The final diagnostic criteria used in this research project are presented in Chapter 3 of this paper.
They are based on the criteria used in the previous Barwon IBD epidemiology study, and also
incorporate the Copenhagen diagnostic criteria outlined above.

2.2.4 Disease Classification and Activity Assessment Tools

Many methods have been developed to assist in classifying the different forms of IBD, and to
accurately assess the level of disease activity present. Unique tools have been developed for both
adults and children, and for CD and UC. These tools are useful for both defining IBD burden in
specific patients, and for gaining objective, reproducible measures of disease activity over time.
Whilst primarily developed as outcome measures for therapeutic drug trials, they also allow for
useful comparisons of disease features and outcomes from different population-based study
cohorts.

CD

A number of classification systems have been developed to define phenotypes and different stages
in the disease evolution of CD. Earliest attempts were made by Farmer et al in 1975, based on
anatomical location of disease (Farmer et al., 1975). Subsequently, in 1988 Greenstein et al defined
behavioural features with regard to perforating or non-perforating disease activity (Greenstein et al.,
1988). A composite of these two factors resulted in the Rome classification system, first described in
1992 (Silverberg et al., 2005). Simpler, more clinically applicable systems have been developed since
that time, with the Vienna classification, and the subsequent Montreal revision, being the most
widely used. The initial Vienna classification was developed by a working party of the World
Congress of Gastroenterology in 1998, and then published in 2000 (Gasche et al., 2000). It considers
three categories: age of onset (A), disease location (L), and disease behaviour (B). Perianal disease
was included in this classification as a penetrating, or fistulising, complication. The subsequent
Montreal revision of the Vienna classification in 2005 made several key modifications to each of
these categories (Satsangi et al., 2006). Significantly, perianal disease was added as a separate sub-
classification, due to the recognition of a differing disease course of perianal versus internal penetrating complications. This variety of classification methods has important implications when interpreting previous disease evolution studies and comparing them to contemporary studies. Table 2.7 outlines the Vienna and Montreal classification systems (modified from (Satsangi et al., 2006)).

Table 2-7 Vienna and Montreal classification for CD

<table>
<thead>
<tr>
<th>Vienna</th>
<th>Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>A1 &lt; 40 years</td>
<td>A1 &lt; 16 years</td>
</tr>
<tr>
<td>A2 &gt; 40 years</td>
<td>A2 between 17 - 40 years</td>
</tr>
<tr>
<td>A3 &gt; 40 years</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>L1 ileal</td>
<td>L1 ileal</td>
</tr>
<tr>
<td>L2 colonic</td>
<td>L2 colonic</td>
</tr>
<tr>
<td>L3 ileo-colonic</td>
<td>L3 ileo-colonic</td>
</tr>
<tr>
<td>L4 upper</td>
<td>L4 isolated upper disease*</td>
</tr>
<tr>
<td>Behaviour</td>
<td></td>
</tr>
<tr>
<td>B1 inflammatory (non-stricturing/non-penetrating)</td>
<td>B1 inflammatory (non-stricturing/non-penetrating)</td>
</tr>
<tr>
<td>B2 stricturing</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td>B3 penetrating</td>
<td>B3 penetrating</td>
</tr>
<tr>
<td>p peri-anal disease modifier†</td>
<td></td>
</tr>
</tbody>
</table>

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
†"p" is added to B1–B3 when concomitant peri-anal disease is present.

Disease activity assessment is equally as important as a disease classification system for clinical practice. The Crohn's Disease Activity Index (CDAI) is currently the most widely used severity assessment tool used in a variety of clinical and research situations. Originally developed in 1975, the CDAI was designed specifically to measure disease activity changes with response to therapy in the National Cooperative Crohn’s Disease Study (NCCDS) (Summers et al., 1979). The CDAI is
calculated from a composite of clinical, subjective and laboratory indices, with good reliability and reproducibility. However, it has been regarded as cumbersome, particularly due to its reliance on physical assessment and laboratory values (Thia et al., 2011). In 1980, Harvey and Bradshaw published a simpler, equally reproducible index of CD activity, the Harvey Bradshaw index (HBI) (Harvey and Bradshaw, 1980). This has subsequently been shown to correlate adequately with the CDAI (Best, 2006).

The length of these two activity measures, and the need for clinical examination and laboratory measures, further prompted the development of the simplified short-CDAI. This was produced by incorporating features of the traditional CDAI, in addition to the Inflammatory Bowel Disease Questionnaire (IBDQ) (Thia et al., 2011). The short-CDAI is based on three variables only taken over seven days; the number of liquid or soft stools per day, daily abdominal pain ratings, and a sum of total wellbeing. Recent work by Thia et al has assessed this new, simplified index with regard to its validity, reliability, and responsiveness, demonstrating good correlation (Thia et al., 2011). However, limitations with this score exist. It does not adequately assess perianal symptoms, obstruction due to stricturing disease, or assess disease activity in patients with a stoma. Additionally, it has only been validated in patients with mild-moderate ileal or ileocolonic disease.

An alternative method of assessment of disease severity has been made based upon observed medication use and surgery. Silverstein et al published data on treatment inferred disease severity (Silverstein et al., 1999). These authors defined severity from 1-6, where 1 represents no IBD medication use through to 6 as death from any cause. This severity scale was developed in a large population-based cohort from North America, and has subsequently been used in other population-based longitudinal studies including the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD) (Wolters et al., 2007).

UC

In contrast to CD, there has been relatively little research into development of classification tools for UC. A working party convened in 2006, and concluded that developing a system of classification for UC was of high importance, with particular regard to the need to accurately classify changes in phenotype over time, specifically related to disease behavioural observations. The proposed Montreal classification system for UC is presented in table 2.8 (adapted from (Satsangi et al., 2006)).
Table 2-8 Montreal classification of extent of ulcerative colitis (UC)

<table>
<thead>
<tr>
<th>Extent</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Ulcerative proctitis: Involvement limited to the rectum (proximal extent of disease is distal to the rectosigmoid junction)</td>
</tr>
<tr>
<td>E2</td>
<td>Left sided UC (distal UC): Involvement limited distal to the splenic flexure</td>
</tr>
<tr>
<td>E3</td>
<td>Extensive UC (pancolitis): Involvement extends proximal to the splenic flexure</td>
</tr>
</tbody>
</table>

A publication in 2007 described over 13 different scoring systems in use for UC severity assessment (D’Haens et al., 2007). Truelove and Witt were the first to attempt to quantify UC activity in 1955, by defining mild, moderate and severe disease (Truelove and Witt, 1955). In the early 1980’s the Mayo Score was developed as a composite of clinical and endoscopic features (Schroeder et al., 1987). This score has been used in many studies since, particularly relating to therapy. The simplified clinical colitis activity index (SCCAI) subsequently evolved as a purely non-invasive activity index, covering six clinical questions only. An age-specific paediatric score was also developed at this time, the paediatric ulcerative colitis clinical activity index (PUCCAI). Satsangi et al proposed the Montreal severity assessment, outlined in table 2.9 (adapted from (Satsangi et al., 2006)).

Table 2-9 Montreal classification of severity of ulcerative colitis (UC)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0</td>
<td>Clinical remission: Asymptomatic</td>
</tr>
<tr>
<td>S1</td>
<td>Mild UC: Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)</td>
</tr>
<tr>
<td>S2</td>
<td>Moderate UC: Passage of more than four stools/day but with minimal signs of systemic toxicity</td>
</tr>
<tr>
<td>S3</td>
<td>Severe UC: Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h</td>
</tr>
</tbody>
</table>

*ESR - erythrocyte sedimentation rate.

It is important to note that none of these scoring systems have been formally validated with regard to their biometric properties with specific reference to their responsiveness, reliability and validity, nor have they been standardised with regard to their utility in prospective epidemiological assessments (Cooney et al., 2007).
2.3 EPIDEMIOLOGY OF IBD

The study of CD and UC epidemiology has been central to progressing our understanding of these complex chronic inflammatory conditions. The study of large populations with these conditions has provided unique and valuable insights, including defining the magnitude of the problem (related to incidence and prevalence), and observing how changes in disease rates have occurred over time. Geographic and socioeconomic influences have been observed to be important in IBD epidemiology, and studying these populations has provided evidence on risk factors linked to disease development. There is still, however, a significant amount of work to be done in this field.

While theories related to urbanisation and westernisation have been proposed to account for observed regional variations in IBD, a definitive explanation is still lacking. The influence of Vitamin D on longitudinal and latitudinal variations within regions is under investigation. Interesting and largely unexplained differences between paediatric IBD and adult IBD populations are now being observed. Furthermore, it is not clear whether the advances in IBD therapeutics are translating in to alteration in disease evolution. Finally, considerable work with respect to IBD disability, productivity impairment and health related costs, is still required. To answer these questions we are now entering a new era of large-scale, well designed population-based epidemiological studies, with an emphasis on trans-border collaboration.

2.3.1 The History of Epidemiology Insights in IBD

Globally, rates of IBD have increased significantly over the last 50 years (Vind et al., 2006). Trends from Europe and North America suggest that the incidence of UC rose through the early to mid 20th century before stabilizing, while CD has continued to increase throughout the century (Logan and Bowlus, 2010). A population-based publication from Denmark clearly demonstrated the rate of IBD continued to rise in the local Copenhagen region as recently as 2005 (Vind et al., 2006). Data from developing countries suggests a continued and rapid rise (Loftus Jr, 2004). Previous observations suggest that the increase in incidence of ulcerative colitis precedes the increase in incidence of CD by 10-20 years, although the reason for this is unclear (Loftus Jr, 2004).

The majority of epidemiological literature in IBD has traditionally originated from North America, the United Kingdom and Western Europe. These regions have previously demonstrated high rates of IBD, and also have advanced health care systems with mechanisms in place to assist with national disease surveillance. Some data began emerging from Central and Eastern Europe in the early 1990’s, suggesting a significantly lower rate of IBD when compared to their more western counterparts (Vucelj et al., 1991). However, more recent work from this region suggests rates are in fact rising. For example, IBD rates in Hungary have recently been shown to be comparable to those in Western Europe (Lakatos et al., 2011). Dramatically increasing rates of IBD have also been more recently observed across parts of Asia, where historically very low rates of disease had been previously seen (Thia et al., 2008).
Specific geographical and age related variations are further discussed in sections 2.3.3 and 2.3.4.

2.3.2 Defining IBD Incidence and Prevalence: What are they and why are they important?

Disease incidence is defined as the frequency of new cases of an illness that are diagnosed during a specified time period in a defined population. Conventionally in IBD literature this has been expressed as cases per 100,000 person years. This figure can be further divided into sub-groups based on gender and age as required. The importance of incidence calculation lies in its ability to assess trends in disease over time. Disease prevalence is defined as the number of people living within a population who have the specified disease at any one point in time. Prevalence is particularly relevant with respect to chronic diseases, with patients living with their illness for many years. The study of disease prevalence provides unique insights into disease burden within society, and is crucial for planning health care provision and resource allocation. Estimation of incidence and prevalence rates generally result from descriptive epidemiology research (Webb et al., 2006).

Accurate information on disease incidence and prevalence relies on the collection of high quality clinical information. This requires a number of important epidemiological considerations (Webb et al., 2006). Firstly, it is crucial to define and standardise how the diagnosis of the condition is made. By strictly adhering to diagnostic definitions, researchers are able to reduce the inclusion of false positives and the exclusion of false negatives from the final calculation. Using standardised diagnostic criteria thus allows valid comparisons between studies.

This is a particular issue, for example, when basing the diagnosis of a condition only on a computer generated code, rather than clinician derived case identification and cross-referencing. This has relevance when reviewing previously published IBD epidemiology studies, some of which have relied only on numerical patient identifiers cross referenced against various clinical databases, including hospital discharge coding searches or insurance claims (Stausberg et al., 2008).

For example, Barton et al showed a three-fold increase in CD in Scottish children from 1968 – 83, to a final rate of 2.29/100,000 per year (Barton et al., 1989). These data were based on research linked to hospital admission data utilising International Classification of Disease (ICD) codes relevant to IBD. After a partial review of some, but not all, cases in this study, it was revealed that incorrect documentation of coding occurred in 11 out of 83 CD diagnoses and 13 out of 61 UC, with an overall incorrect coding rate approaching 17%. A recent Danish publication examining adherence to medical treatment during pregnancy for women with UC found that around 10% of cases initially derived from their Regional Patient Administration System did not fulfil diagnostic criteria for a diagnosis of IBD when individual medical records were examined more closely (Julsgaard et al.,
2011). Older data from the same region found slightly higher concordance rates with coding and clinically confirmed IBD criteria, with a 6% false identification rate reported (Fonager et al., 1996).

Secondly, one must have a relatively stable and clearly-defined population in which to study an illness. This population represents the number of people at risk of developing the condition, becoming the denominator in calculating final incidence and prevalence rates (Webb et al., 2006). For instance, if the geographical boundaries of an area are poorly defined, or there is significant population movement in and out of the study area in question, the final incidence and prevalence calculations will be unreliable due to the risk of over or under-estimation. This could be a particular issue in some Asian IBD studies, with high density and very mobile populations making the definition of the at risk population difficult.

Thirdly, for incidence figures to be truly accurate, all new cases from an area need to be identified. This is referred to as completeness of case ascertainment (Webb et al., 2006). If this is not achieved, then final disease rates will be under-estimated. This has been a particular problem in the past, when disease incidence and prevalence rates have been estimated based on hospital sourced disease data, rather than considering multiple sources of patient referrals, also known as the technique of capture-recapture methodology (Wilson et al., 2010, Gismera and Aladrén, 2008).

Adhering to these strict criteria when planning methodologically-sound, population-based epidemiological research, remains a challenge. There have previously been hundreds of publications describing IBD incidence and prevalence from around the world, however the methodology employed in these works has varied widely. There is, therefore, a risk that some of the variation in IBD incidence and prevalence rates observed between studies may reflect differences in research design rather than true variations. This is particularly relevant when comparing more recent results to historical data. Contemporary epidemiological studies have generally used more robust methods for disease frequency estimation, and hence produce more reliable results. Recognition of the importance of sound research methodology, and identifying the limitations of previous research, form an important part of planning future population-based epidemiology research.

2.3.3 Geographical Variability in IBD Epidemiology

There is a great deal of variation in the global published literature regarding IBD incidence and prevalence (Baumgart et al., 2011). A review of the most robust data currently available reveals global IBD incidence rates range from 0.5 to 29.3 per 100,000, with rates for CD ranging from 0.5 to 17.4 per 100,000, and for UC from 1.2 to 13.4 per 100,000. Prevalence rate estimations for total IBD range from 7.0 to 444 per 100,000, with CD and UC rates ranging from 1.9 to 271 per 100,000, and from 6.0 to 249 per 100,000, respectively. Rates for IBDU remain relatively low, with incidence rates ranging from 0.8 to 1.1 per 100,000, and prevalence rates ranging from 3.0 to 8.0 per 100,000.
Examples of global variations in IBD rates are provided in figure 2.1, a screen shot from the current EPICOM website.

The reasons for the variability in published IBD incidence and prevalence data are multifactorial. It is highly likely that true geographical differences do occur, for instance the low rates of IBD previously observed throughout Asia when compared to Europe and North America (Thia et al., 2008). However, it remains important to consider the widely different study designs, each with their own inherent flaws and biases. Some are retrospective reviews, while others rely on prospective case identification. In addition, a wide variety of reference populations have been used, ranging from hospital-based to true community-based populations. Case ascertainment methods have varied widely, from health insurance and hospital coding data utilization to clinician lead, prospective case identification and validation. Outside of Australasia, the most methodologically robust data have been published from Western Europe and North America, including both the USA and Canada. This data has largely been produced through large-scale, prospective population-based cohorts.
The following sections review the epidemiology literature from different geographical regions, starting with the largest studies from traditionally high rate countries.

**Pivotal Epidemiological Studies**

As previously outlined, research from Europe, North America, and more recently Australia and New Zealand, have produced the most reliable and robust data on IBD incidence and prevalence rates. This reflects on the fact that these regions have the highest rates of IBD when compared to other parts of the world, and also on the fact that the health systems from these regions are sophisticated enough to support large-scale population based epidemiological research.

**Europe**

Reliable data began to emerge from Europe in the late 1980's and early 1990's. Vucelj et al published UC rates from Zagreb, Yugoslavia, in 1991 (Vucelj et al., 1991). In a relatively small geographical region, this group reviewed ten years of data on ulcerative colitis from 1980-1989. The study included outpatients and inpatients, revealing a mean annual incidence rate of only 1.5 per 100,000, and a prevalence rate of 21.4 per 100,000. They did not observe any change in the incidence of ulcerative colitis over the 10 year study period. However, several weaknesses in these data are evident. No information was provided on population definitions or estimates, local migration rates, diagnostic criteria, or how complete case ascertainment was.

In 1995 Thomas et al published incidence rates for CD in Cardiff, Wales, with an overall rate of 5.9/100,000 (Thomas et al., 1995). They found the highest rates in the 15-34 year old age group. While most of their data was based on hospital coding searches, they also performed clinical record reviews, GP questionnaires and pathology searches, improving the completeness of case ascertainment and allowing a more accurate population-based estimate of disease frequency.

An early attempt at assessing changes in IBD rates at a population-based level was published in the late 1990’s by Russel et al (Russel et al., 1998). Many aspects of this important early epidemiological study have relevance to the methodology of this current research thesis. Firstly, the authors assessed retrospective data from the Leiden region of Holland from 1978 – 81, estimating incidence rates for CD 3.9/100,000, and for UC 6.6/100,000. They then undertook a prospective, population-based study to re-assess local rates. The prospective study, from 1991-94, was based on a geographically defined region in South-Eastern Holland, with a study population of 642,240. The area was serviced by six principal hospitals. The primary case source was local clinicians, including gastroenterologists, physicians, surgeons and paediatricians, in addition to 300 General Practitioners. The research team was extensive, with 9 clinician researchers and a team of medical students involved in data collection. Hospital coding, pathology and endoscopy database searches were also performed. Regular meetings were held with the local clinicians throughout the study period. At the conclusion of the study, they found incidence rates for CD 6.9/100,000 per year, and
UC 10/100,000, with the authors concluding there had been a significant rise in local IBD rates. However, this study highlighted a number of important issues relevant to comparing disease rates. Problems included an imprecise definition of the study population or geographical region, deficiencies in case ascertainment, variability in diagnostic definitions, and issues related to the validity of comparing prospective data to retrospective information. Another important aspect to emerge from this research was the large amount of work required to perform and maintain prospective population-based research, requiring a large team of researchers.

In 1994 Gower-Rousseau et al published high quality population-based data from Northern France (Gower-Rousseau et al., 1994). Their prospective study, from 1988-90, incorporated three geographically defined regions. The population of over 4 million was accurately defined based on French National census data. The collaborative work involved 125 gastroenterologists across the region, and was co-ordinated by 11 hospital-based IBD clinicians. Phone and mail contact was maintained with the local gastroenterologists, and cases were verified by record review. They calculated incidence rates for CD of 4.4/100,000, and for UC of 3.2/100,000. To assess the completeness of case capture, the authors performed an internal case ascertainment validation study. This occurred over a 12 month period, and involved contacting the 498 GPs, in addition to all radiologists, pathologists, surgeons and paediatricians. When cross-referencing cases identified with these additional methods, only 3 extra cases were found, suggesting that 96.5% of new cases were identified by specialist gastroenterologists alone, further validating the final incidence and prevalence rate calculations.

Chouraki et al then published a follow-up study from this same region in 2011 (Chouraki et al., 2011). Ongoing case ascertainment and collection continued from 1990, with all new case details recorded centrally in the EPIMAD registry. The study area was expanded, and by 2007 included over 5.7 million people, or 9.3% of the total French population. Data on local migration patterns revealed a very stable population. In 2007 CD incidence rates had increased by 29% to 6.7 per 100,000, with the largest increase of 71% observed in the 10-19 year age group (6.5 to 11.1/100,000). Interestingly, UC incidence declined from 4.3 per 100,000 in 1988-90 to 3.4 per 100,000 in 2007.

There has been a large volume of research regarding IBD epidemiology from the Scandinavian countries. Favourable population characteristics include relative geographic isolation, and robust health care systems that allow accurate disease-specific data extraction.

Iceland is one such region with several features that allow high quality epidemiological research, including geographic isolation and very low rates of migration resulting in a very stable population (Björnsson et al., 1998). In addition, healthcare is provided through only a limited number of hospitals, making disease tracking relatively easy and providing the opportunity for reliable long-term rate changes to be studied. Björnsson et al published data on IBD across Iceland in 1998 (Björnsson et al., 1998). Firstly, a retrospective study from 1970 revealed incidence rates of
5/100,000 for UC and < 1/100,000 for CD. Subsequently, nationwide comparative studies between 1950 and 1989 showed a continuously rising incidence of IBD. Then, in 1998, a prospective study performed from 1990-94, was published. This revealed an incidence rate for CD of 5.5/100,000 and UC 16.5/100,000, confirming a significant rise in IBD incidence across Iceland.

Denmark remains at the global forefront of research relating to IBD epidemiology for a number of reasons. Geographical isolation, and perhaps more importantly the unique health identification numbers allocated to each citizen, have allowed careful and accurate observations on the entire Danish population over time. In 1991 Langholz et al published local data with UC incidence rates of 8.1/100,000, and prevalence of 161/100,000 (Langholz et al., 1991). They demonstrated a steady increase in both rates from 1960-1987, and also illustrated a bimodal distribution in age of onset of UC in men, with a second peak later in life.

Researchers from Copenhagen compared disease rates between inception cohorts from 1962-1987, and to a more recent cohort from 2003-2004 (Vind et al., 2006). The mean annual incidence of CD in Copenhagen county increased from < 1/100,000 in the 1960’s, to 8.6/100,000 in 2003-04. Results were similar for UC, with rates increasing from 6.9 to 13.4/100,000. Strengths of this data include the prospective nature of data collection, the use of strict diagnostic definitions, and high levels of clinician involvement in case identification and validation.

Valuable insights into IBD behaviour have also been possible from longitudinal observation of these population-based cohorts. Jess et al demonstrated colectomy rates of 6% within 1 year of diagnosis for UC patients (Jess et al., 2007). They also showed changes in the proportion of patients with CD, a reduction in time from symptom onset to diagnosis, an increase in the median age of diagnosis for UC, and changes in the patterns of prevalence of upper GI and colonic involvement in CD. They also observed reduced surgical rates for CD, but not UC, in the later cohorts. These novel insights demonstrate the usefulness of well-designed, population-based cohorts.

Moum et al published prospectively collected population-based incidence data from four counties in South-Eastern Norway from 1990-93, showing CD incidence rates of 5.8/100,000 and UC incidence rates of 13.5/100,000 (Moum et al., 1996). With regards to CD, a peak incidence of 11.2/100,000 was seen in the 15-24 age group. This population has subsequently formed the basis of the IBSEN cohort (the Inflammatory Bowel South-East Norway cohort). A follow-up study of the initial incident cases after 12-24 months showed that approximately 10% of patients were re-classified with regards to either their diagnosis or phenotype (Moum et al., 1997a). This point highlights the difficulty in confirming an accurate diagnosis of IBD in the absence of a single reliable diagnostic test, and the importance of adhering to recognised diagnostic criteria for future inception cohorts.
The IBSEN group has recently published follow-up data on 10 years of longitudinal observation (Solberg et al., 2009). This includes, for UC, relapse rates of over 80%, a colectomy rate of 9.3% and disease location extension in around 20% of the original inception cohort.

Before considering the data from North America, it is worth reviewing the pattern of incidence and prevalence observed within Europe, and the influence of longitude and latitude. Within Western Europe, IBD appears at least three times more common in northern latitudes than in the south (Wolters et al., 2007). In the early 1990’s, all incident IBD cases from 20 European centres were prospectively enrolled in the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD) study. Rates of both CD and UC from the more northern centres were higher than from the southern centres (UC rates 40% higher and CD rates over 80% higher with more northern latitudes) (Shivananda et al., 1996). However, some issues regarding result validity were raised, and after correcting for variation in tobacco consumption and socioeconomic status, the initially observed differences were less clear.

Geographical influence on IBD rates is the subject of a current large-scale study being undertaken across 27 countries spanning Western and Eastern Europe, with coordination through the European Crohn’s and Colitis Organisation (ECCO) epidemiology committee (Epicom) (Burisch et al., 2011). Results are expected in 2012/2013, and until then the influence of longitude and latitude on IBD remains uncertain.

**North America – Canada and USA**

Canada has a long history of large-scale and methodologically robust epidemiology research. One example is the Manitoba Health Insurance Database, based on unique patient identification numbers used to access local health care services (Blanchard et al., 2001). Researchers extracted IBD-related information from this database in 2001, from a population of 1.4 million. From 1987-1996 incidence rates for both CD and UC were 15.6/100,000. By reviewing socioeconomic data, the authors were also able to link higher rates of disease to higher median household incomes and smaller family sizes.

In 2006, Bernstein and colleagues estimated incidence and prevalence rates for IBD based on similar healthcare database searches over 5 Canadian regions including British Columbia, Alberta, Saskatchewan, Nova Scotia, in addition to the Manitoba region mentioned previously (Bernstein et al., 2006). They found regional variations in incidence rates for CD ranging from 8.8/100,000 in British Columbia through to 20.2/100,000 in Nova Scotia, with prevalence rates approximately 15-20 times that of the incidence rate (range 161-319/100,000). Similarly, for UC the incidence rates were 9.9/100,000 in British Columbia up to 19.5/100,000 in Nova Scotia, with prevalence ranging from 162 – 249/100,000. When extrapolated to the entire Canadian population, it was estimated that 111,000 people were living with IBD in 2006, representing 0.5% of the total population.
The USA has a long history of publications related to IBD epidemiology, ranging from hospital-based to population-wide studies. Research to emerge from Baltimore in the early 1980’s demonstrated rising rates of IBD (Calkins et al., 1984). A series of three hospital-based studies from 1960-1979 showed an increase in incidence of both CD and UC, from 1.2/100,000 and 1.3/100,000 respectively in 1960-63, to 2.9/100,000 and 3.39/100,000 in 1977-79. The study was undertaken through 24 hospitals in the Baltimore area, and relied on hospital diagnostic coding data. While the methodology used during the three time periods was the same, and the population at risk was defined through census data, only IBD cases requiring hospital admission were captured, likely under-estimating true local disease rates.

Higher quality American IBD data has subsequently been published. The most current prevalence rates for adults range from 129-201/100,000 for CD and 191-238/100,000 for UC, with a total IBD prevalence rate of 388-444/100,000, translating into approximately 1 million US citizens living with IBD (Herrinton et al., 2007, Kappelman et al., 2007). These figures were based on the health insurance claims of approximately 9 million people over 33 states, in addition to coding data and pharmacy dispensing records, and were further supported by a large-scale population-based study from Olmstead County in Minnesota (Loftus et al., 2007).

As within Europe, regional differences within the USA relating to latitude and longitude have also been observed for IBD. Prevalence rates in southern states are lower than in northern states (Herrinton et al., 2007, Kappelman et al., 2007). Further evidence of a latitude gradient comes from the recent publication of IBD incidence rates among US women derived from a long-term observational study (Khalili et al., 2012). Women residing in more northern latitudes had significantly higher rates of IBD than those from more southern states.

Asian IBD Epidemiology

Prior to 30 years ago, IBD was almost unheard of across Asia. Reference to IBD was largely through small isolated case-reports. More recently there has been a rise in IBD incidence and prevalence across Asia (Goh and Xiao, 2009, Hou et al., 2009). While detailed information remains limited, with IBD data published from only a small number of Asian countries, the rise in the incidence of UC, and to a lesser extent CD, appears to be real. The rise in IBD seems to parallel regional development, economic growth, westernisation and increasing affluence (Ouyang et al., 2005). In most parts of Asia, UC still predominates over CD, a pattern of disease burden that was traditionally seen in North America and Europe toward the end of last century (Leong et al., 2010). This suggests that a phenotypic change from UC to CD occurs over time in emerging populations of IBD.
A number of barriers exist when planning epidemiological research in the Asian region (Leong et al., 2010). Firstly, significant financial factors, a lack of resources, and poorly co-ordinated health-care delivery exist in many parts of Asia. Some regions lack access to many health care services, including endoscopy, pathology and medical imaging services, required to confirm a diagnosis of IBD. Local population movement is significant, impacting on the ability to define the true population at risk. Medical practitioners with little experience in IBD diagnosis and management risk missing possible new IBD cases. Additionally, many patients throughout Asia prefer to seek advice from traditional and alternative health practitioners, rather than pursuing Western medicine. Finally, very high rates of infectious colitis are seen throughout Asia, including intestinal Tuberculosis, with the potential to confound the accurate diagnosis of IBD (Goh and Xiao, 2009). All of these factors may have impacted on the previously low IBD rates reported from Asia.

The first reports of IBD emerged from Asia in 1969, with a case report from Fung and Khoo on two patients with UC (Fung and Khoo, 1969). It was a further 20 years before Goh et al then reported in abstract form 12 patients with CD, concluding that the disease was still very uncommon in this region (Goh et al., 1990). Data from China has subsequently suggested a dramatic rise in IBD recognized in these regions, particularly with regard to UC, with a three-fold increase in reported cases (Jiang and Cui, 2002). Thia et al performed a comprehensive MEDLINE search from 1950 through to December 2007 related to IBD in Asia (Thia et al., 2008). Of the 298 articles initially identified, they reviewed a subset of 151 studies focusing on defined factors including incidence, prevalence, clinical features, disease course and complications in Asian populations. They noted a rapid rise in publications relating to Asian IBD epidemiology, with 4 studies published between 1960-69, compared with 57 studies published between 2000 and 2007. Secondly, they found that the strongest, longitudinal data had been produced from Korea, Japan and Hong Kong, with data from these East Asian countries suggested a continued rise in the incidence of both CD and UC.

Asian IBD studies have revealed some novel findings. One interesting observation is the lack of familial clustering in Asian populations, in contrast to the stronger family association with the disease seen in the West. This may be related to small case numbers, with most authors suggesting that as the incidence and prevalence of IBD increases in Asia, a similar family association that has been observed in Western populations will also emerge in Asia (Leong et al., 2010). Secondly, within Asia it is clear that certain ethnic subgroups are more prone to developing IBD than others. For instance, Indians living in South-East Asia have higher rates of disease than Chinese and Malays living in the same region (Goh and Xiao, 2009). While it is unclear which specific factors are responsible for this, both host genetics and environmental influences (including diet and microbes) are likely to play a role (Prideaux et al., 2012).

As previously mentioned, there has been extensive heterogeneity in the quality of epidemiological research from Asia. An attempt to control for these variations has resulted in the design of a large-scale, multi-centre, prospective epidemiology study which commenced in April 2011, with the hope of accurately comparing IBD incidence among various defined regions throughout Asia. The study
design allows for prospective disease evolution observations in a cohort of newly diagnosed Asian patients, in addition to a review of specific host genetic and environmental factors central to IBD developing in these populations (personal communication Siew Ng, Hong Kong). Results from this research thesis will form a comparison group for this large-scale Asian study, with final results planned for 2013-2014.

Australia/New Zealand Research

There have been relatively few IBD epidemiology studies published from the local region. Two Australian hospital-based studies have previously examined IBD incidence rates. Firstly, a prospective study from 1987 involving six hospitals in Melbourne, Victoria, revealed local case numbers for IBD were comparable with published international figures (McDermott et al., 1987). A major weakness of this study was that the population at-risk was not defined or quantified, resulting in a lack on an accurate denominator with which to calculate true incidence rates. It was also difficult to confirm if the cases were incident, as any IBD patients presenting to the hospital were included, regardless of when their diagnosis had been made.

The second Australian study involved a retrospective review conducted through the Royal Children’s Hospital and Monash Medical Centre, also in Melbourne, Victoria (Phavichitr et al., 2003). Their results suggested a significant increase in the incidence of CD over the 31-year period that was studied. The incidence of CD in children, defined as aged 16 years or less, at the end of the study period in 2001 was 2.0/100,000, By comparison, a rate of 0.13/100,000 was estimated from data from the 1970’s, with the change representing an increase of over 15 fold. While the two hospitals involved were the major referral centres for paediatrics IBD in the state, issues relating to selection bias and case ascertainment rates should be considered when interpreting this data. In addition, this time period also saw a rise in access to endoscopy, which may have facilitated a diagnosis of IBD in more children at the end of the study period. Finally, case identification was based on retrospective ICD coding data gathered from hospital databases, without clinical diagnostic criteria being considered. This may have been another potential source of error reducing the reliability of this published data.

In 2004, a landmark population-based study by Gearry et al published from Canterbury in New Zealand revealed a high incidence of IBD, with local rates comparable to the highest reported rates from North America or Europe at that time (Gearry et al., 2006). The researchers found local incidence rates for total IBD, CD and UC were 25.2, 16.5 and 7.6/100,000 respectively. The point prevalence rates for June 1\textsuperscript{st} 2005 for total IBD, CD and UC were 308.3, 155.2 and 145.0/100,000 respectively. This study had a number of strengths. To ensure a high level of case ascertainment patients were prospectively collected from several sources, including self-referral, clinician-referral and hospital/pathology coding searches. The records of two representative GP providers were also manually searched. Through this capture-recapture technique it was estimated that the study was able to identify over 90% of patients with IBD living in the area during the period of study,
representing a high level of case ascertainment. Diagnostic validation was made with reference to
strict internationally recognised criteria for the diagnosis of IBD. The authors were also able to
maintain a database of phenotypic details on these patients as part of a broader Canterbury
Inflammatory Bowel Disease Project, allowing for disease follow-up, disease evolution review, and
assessment of the role of lifestyle factors, diet and genetics on the development of IBD. This
research has already allowed several important epidemiological insights, including identification that
perianal disease is a risk marker of severity for future complicated phenotypes, the relatively low
incidence and prevalence of IBD among native Maori populations, and evidence for the protective
role of early breastfeeding against IBD onset in later life (Gearry et al., 2006, Gearry et al., 2008,
Gearry and Day, 2008, Gearry et al., 2010).

Most recently, Wilson et al undertook a similar population-based study in the Geelong region in
South-Western Victoria (Wilson et al., 2010). This study was completed in 2008, and produced
Australia’s first prospective population-based IBD incidence data. The researchers found rates that
were similar to those found in the New Zealand study, with crude incidence rates for IBD of
29.3/100,000, CD 17.4/100,000 and UC 11.4/100,000. Barwon, with a population of approximately
260,000, has many attributes that support high quality epidemiology studies, and several large-scale
chronic disease research projects have previously been completed in the region.

The Barwon study by Wilson et al was a 12-month prospective study that had a robust capture-
recapture methodology. Incident IBD case data was collected from several sources including local
gastroenterologists, surgeons, paediatricians, pathology providers and endoscopy services. An initial
survey of the regions GPs was also undertaken to gage their local referral pattern, showing that the
vast majority referred to GI specialists within their area. A further strength of this study was that
strict, internationally accepted case definitions were used for IBD identification, with a single
investigator reviewing all cases at 2 separate time points in an attempt to validate and confirm true
incident cases. Weaknesses include a limited 12-month data collection period, a relatively small
population at risk when compared to other similarly international work, and also the inability to
collect identifiable data to prospectively follow-up these patients. Prevalent cases were also
excluded, so no accurate prevalence figures could be calculated.

2.3.4 Age Variability in IBD Epidemiology

Although IBD can be diagnosed at any age, around one quarter of new diagnoses will be made
before the age of 20 years (Henderson et al., 2011). As with adult data, published rates of paediatric
IBD vary worldwide. A spectrum of global paediatric IBD rates are presented in table 2.10.
Table 2-10 Paediatric Global IBD Incidence rates (per 100,000).

<table>
<thead>
<tr>
<th>Region/Author/Year</th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbourne, Australia</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Pravichitar et al 2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>6.4</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Jakobsen et al 2007-09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copenhagen, Denmark</td>
<td>-</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Vind et al 2003-05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>7.0</td>
<td>2.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Tusenen et al 2003</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Finland</td>
<td>15.0</td>
<td>5.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Lehtinen et al 2010</td>
<td></td>
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</tr>
<tr>
<td>Northern France</td>
<td>-</td>
<td>5.9</td>
<td>-</td>
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<tr>
<td>Chouraki et al 2006-07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minnesota, USA</td>
<td>-</td>
<td>3.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Loftus et al 1990-2000</td>
<td></td>
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<td>Wisconsin, USA</td>
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<td>Kugathasan et al 2003</td>
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<td>Scotland, UK</td>
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<td>Henderson et al 2003-2008</td>
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Whilst a small prospective population-based study from South Wales published in 2006 showed a local plateau in rates of both CD and UC in Welsh children (Ahmed et al., 2006), the majority of the paediatric IBD literature suggests increasing rates of paediatric IBD. This observation is supported by evidence from a number of disease behaviour studies in addition to recent systematic reviews.

A small hospital-based study from Melbourne, published in 2003, demonstrated a 15-fold increase in paediatric CD incidence over 31 years of observation (Phavichitr et al., 2003). A well designed, collaborative population-based study from Wisconsin in the USA published in 2003, examined all new cases of IBD reported over a two year period by 21 paediatric gastroenterologists (Kugathasan et al., 2003). The incidence of IBD in their paediatric population was 7.05 per 100,000, with CD occurring twice as commonly as UC (4.7 versus 2.1 per 100,000). Significantly, this study was the first population based study of IBD incidence to emerge from North America, with all previous historical data based on tertiary hospital information only.
A more recent publication by Lehtinen et al examining IBD incidence among Finnish children also showed a significant rise in disease rates (Lehtinen et al., 2010). Using Finland insurance database records, these authors demonstrated a rise in IBD incidence from 5/100,000 in 1987, to 15/100,000 in 2003, representing an increase of 6.5% per year. A similar trend toward increasing IBD rates has also previously been observed in paediatric populations from Canada (Benchimol et al., 2009). However, when examined by different age groups these authors only observed a statistically significant rise in the 0-9 age group, with stable rates observed in the 10-16 age group.

Further evidence of rising rates of paediatric IBD includes a recently published systematic review from 2010 (Benchimol et al., 2010). After assessing global publications on paediatric IBD, these authors concluded that global rates of paediatric IBD are rising, largely driven by a significant increase in CD. Finally, results of a comparative cohort study were recently published supporting the observation of rising IBD rates in children (Henderson et al., 2011). This Scottish study compared nationwide paediatric IBD incidence rates across Scotland between two time periods, using a range of population-based epidemiology methods. Between 1990-95 (cohort 1) and 2003-08 (cohort 2), a dramatic 76% rise in IBD incidence was documented, with crude rates rising from 4.45/100,000 for cohort 1 up to 7.82/100,000 for the latter cohort. The most striking increase was observed for CD. In addition, there was a statistically significant reduction in the age of IBD diagnosis (from 12.7 to 11.9 years p = 0.003), with a continued male preponderance. The age group between 11-15 years had the highest age-adjusted incidence, with a rate of 16.44/100,000 seen in the second, later cohort.

However, comparing epidemiological results from different regions is prone to error. Factors include a wide range of study designs, a lack of standard diagnostic criteria, and variability in the definition of paediatric age ranges. Within this caveat, some IBD epidemiological trends are worth noting, particularly when comparing paediatric IBD to adult onset disease.

For instance, the ratio of new CD cases compared with UC is approximately three to one in children, higher than that observed for adults (Shikhare and Kugathasan, 2010). In addition, a slight female predominance in adult onset CD has been demonstrated in some studies, while the pattern in children reveals a stronger male bias (Van Limbergen et al., 2008). IBD patterns are often different between adults and children, with colonic disease very common in paediatric IBD cases (Benchimol et al., 2010). Finally, disease extent in children is more likely to extend within the first 2 years from diagnosis when compared to adults (Goodhand et al., 2011). Currently, no specific genetic or environmental factors to account for these differences have been identified, with research in this field continuing.

Patterns of paediatric IBD in Asia are likely to be similar to those described above, although very limited data is available. Paediatric IBD incidence rates among Asian countries have recently been
estimated at 5.2/100,000 (Thia et al., 2008), similar to published Western data. Immigrant studies suggest higher rates among immigrant children from Asia living in Western countries, with rates of up to 15.2/100,000 seen among South-Asian children living in Canada (Pinsk et al., 2007).

2.3.5 Deficiencies in existing IBD epidemiology literature

The key problem encountered when interpreting historical IBD epidemiology data is the extensive variability with regard to study design, with the subsequent impact on the reliability and comparability of the rate estimates produced. It is clear that the most robust data comes from prospective, longitudinal, population-based studies which use clearly defined and validated diagnostic criteria for patient inclusion. Not only do these studies provide the most reliable incidence and prevalence data, over time, they also allow for the study of disease evolution and behaviour observation.

True population-based studies are rare. In a recent review, Peyrin-Biroulet et al performed a literature search for population-based IBD cohorts between 1935 and 2009, and found only 10 such cohorts worldwide (Peyrin-Biroulet et al., 2011a). Of these 10 studies, only five were clinically based and well validated, with the rest based on administrative data. This emphasises the significance of the research undertaken for this thesis project, given that the methodology used will be among the most robust of any IBD epidemiological study previously undertaken.

2.4 IBD BEHAVIOUR, IMPACT AND MANAGEMENT

The following sections will cover issues relating to how IBD evolves in individual patients, the specific impact of disease, and whether current therapeutic approaches have been shown to alter disease progression. The literature regarding IBD disease phenotype, or the observed clinical features and patterns of the disease, will be reviewed. The effect of IBD phenotype on specific outcome measures including surgical rates, hospitalisation, self-reported quality of life, and mortality, will also be examined.

Documenting the evolution of IBD after diagnosis is important. These observations allow an understanding of many aspects of disease pathophysiology. They also provide the clinician with the ability to predict how the disease is likely to evolve in a newly diagnosed patient, and what likely clinical impact the disease will subsequently have. Importantly, this knowledge allows individualised therapeutic strategies to be developed for each patient.

Predicting disease phenotype and behaviour in IBD can be challenging. There is wide heterogeneity in severity of disease at presentation, and subsequent disease course. While disease evolution observations do exist, the majority have been hospital-based and hence subject to significant bias.
Wong and Bressler, 2008). It is important to note that the most reliable data on the disease behaviour of IBD has previously been derived from prospectively established, population-based inception cohorts, observed longitudinally.

2.4.1 Disease evolution of CD

A landmark population-based disease evolution study published in 1999 by Silverstein and colleagues first demonstrated that most patients with CD experienced a relapsing course (Silverstein et al., 1999). However, in this cohort the majority of patients also appeared to experience prolonged periods of remission. Subsequent to this, a systematic review of population based North American cohorts showed much lower rates of prolonged remission, with over 70% of patients experiencing an active, chronic relapsing course (Loftus et al., 2002).

Disease phenotype in CD is traditionally divided into inflammatory, penetrating and stricturing, as outlined previously in the description of the Vienna and Montreal classification systems (Gasche et al., 2000, Satsangi et al., 2006). At the time of diagnosis, the majority of patients have uncomplicated, inflammatory-type disease. For example, in a population-based study from 2003 of 129 newly diagnosed CD patients in Wisconsin, USA, 90% had inflammatory disease at diagnosis, 8% had fistulising disease, and 2% presented with stricturing disease at diagnosis (Kugathasan et al., 2003).

Longitudinal observations of larger IBD cohorts have subsequently revealed that the proportion of patients with complicated disease (penetrating and/or stricturing), increases with time. A landmark paper by Cosnes et al in 2002 demonstrated that, over a 20 year period, the chance of developing complicated disease approached 90% (Cosnes et al., 2002). These results are illustrated below in figure 2.2.
Evidence also suggests that the pattern of disease phenotype at the time of diagnosis of CD can reliably predict the subsequent behaviour of disease. Specifically, rates of relapse, complications and the subsequent need for surgical intervention may all relate to features present at diagnosis. In 2006 Wolters et al, on behalf of the European Collaborative Study Group in Inflammatory Bowel Disease (EC-IBD), published outcome data from over 2000 IBD cases from several European centres (Wolters et al., 2006). A subset of 358 patients had accurate phenotypic data at diagnosis. Outcome data was reviewed 10 years from diagnosis. They found younger age at diagnosis and upper intestinal disease predicted a more severe course. Colonic disease was associated with reduced surgical rates when compared to ileal disease location. However, very low rates of clinical recurrence and surgery were observed across this cohort when compared to other population-based cohorts, suggesting they may have included a milder spectrum of disease. Low rates of participation in the study (only 358 of the original 2201 patients were involved, and only 52% of the original centres from the EC-IBD group participated) may have also influenced the validity of these results.

Other important clinical features at the time of CD onset have also been found to influence disease course. The presence of perianal disease has been shown to independently predict an aggressive disease course (Tarrant et al., 2008, Gearry et al., 2008). Patients with penetrating disease have also been found to have higher re-operation rates than those with non-penetrating disease (Greenstein et al., 1988).
Despite the use of medication to control disease activity, surgical intervention is commonly required in the management of CD. 10-year surgical intervention rates in CD vary widely, with rates 30 years from diagnosis as high as 90% being described from some studies (Caprilli et al., 2006). Despite advances in diagnosis and therapeutics, evidence suggests stable rates of surgery for CD (Cosnes et al., 2005). However, more recent population-based research from Copenhagen suggests falling surgical rates in this population when compared to historical figures, suggesting that improved medical therapy may alter the disease evolution of CD (Vind et al., 2006). This is supported by evidence from the biological literature, suggesting that anti-tumour necrosis factor alpha agents may reduce the risk of surgery in some patient groups (Rutgeerts et al., 2006).

Despite evidence that IBD has a significant impact on morbidity, the impact on mortality is less dramatic. A recent review of several large population cohorts has demonstrated only a very small increase in mortality related to a diagnosis of CD when compared to the general population, with a Standardises Mortality Ratio (SMR) of 1.39 (Peyrin-Biroulet et al., 2011b).

2.4.2 Disease evolution of UC

Data regarding disease evolution of UC are heterogeneous with regards to disease distribution at diagnosis, relapse rates and changes in disease location over time. Direct comparison of disease progression between different cohorts from previous studies is difficult. Furthermore, issues with diagnostic criteria, definition of disease extent, and time points for phenotype assessment further confound the problem.

However, some comparable population-based observational research does exist, with larger UC studies mainly from Europe, North America, and to a lesser extent, Asia. Important disease specific end-points that have received research attention include disease distribution at diagnosis and changes over time, surgical rates, and complication including the development of colorectal cancer. There is limited local Australian data regarding UC phenotype at diagnosis or changes over time.

The IBSEN Study, described previously, was based on 10-year observational data of an inception cohort of 519 patients (Solberg et al., 2009). At the end of 10 years, 423 completed follow-up (82%). Relapsing symptoms were seen in over 80%, however most of the activity was observed within 5 years from diagnosis. 50% were relapse free in the last 5 years of follow-up. Approximately 20% of patients who initially had limited proctitis or left sided disease, had documented extension of their disease during the follow-up period.
Colectomy rates have been used as an important outcome measure in UC. Rates from Western studies from the 1990’s ranged from 3-10% at 1 year, 8-20% at 5 years, and up to 24-34% at 10 years from diagnosis (Thia et al., 2008). Vind et al demonstrated a colectomy rate of 6% within the first year from diagnosis in a population-based cohort from Denmark (Vind et al., 2006). More recent data suggests colectomy rates may be falling, with data from the IBSEN group showing a colectomy rate of only 9.8% after 10 years (Solberg et al., 2009). This group also highlighted factors predicting a higher risk of colectomy in their cohort, including persistently elevated ESR and more extensive disease at diagnosis.

A review of Asian UC epidemiological data from 2008 revealed a similar pattern of disease distribution at diagnosis when compared to Western cohorts (Thia et al., 2008). Proctitis and left sided colitis accounted for the majority of cases (55% to 75%), while extensive or pancolitis at diagnosis ranged from 18.1% to 45.5%. Similarly, relapse rates also appear similar across Western and Asian populations. Relapse rates in Asian UC patients ranged from 30% after 1 year up to 88% after 10 years, although the wide range may reflect on the variable quality of data analysed. Observations from a Korean IBD hospital-based cohort suggest disease location extends in approximately one third of patients within 5 years and up to half of patients by 10 years from diagnosis (Park et al., 2007). These are slightly higher than rates quoted from the previously described IBSEN cohort from Western Europe. This may reflect a selection bias, as the IBSEN group was population-based while the Korean study was hospital-based, thus looking at a population with possibly more severe disease.

The spectrum of paediatric UC phenotype at the time of diagnosis is wide (Benchimol et al., 2011). However, several differences are evident when directly comparing paediatric to adult onset UC. Firstly, disease location at the time of IBD onset is different, with higher rates of more extensive disease in children. For example, a French study of 113 paediatric patients from a geographically defined UC inception cohort showed that 28% had proctitis, 35% had left sided colitis, and 37% had pancolonic disease (Gower-Rousseau et al., 2009). During follow-up of this cohort over a median of 77 months, disease location extended in 50% of patients, again higher than previously described in adult UC patients. In the subgroup whose disease did extend, the colectomy rates were also significantly higher. Overall, the cumulative rate of colectomy was at 8% at 1 year, 15% at 3 years and 20% at 5 years. A recent Danish study of two population-based inception cohorts comparing paediatric and adult UC also revealed higher rates of extensive disease in children, with 70% of paediatric cases having pancolonic disease at diagnosis compared to only 19% of adults in this Danish population (p < 0.001) (Jakobsen et al., 2011). Furthermore, during almost 4 years follow-up of these patients, disease course was more severe in the paediatric cohort, with fewer periods of remission and higher steroid dependency. The reasons for these differences in phenotypes are unknown, however may relate to differences in the function of the naive immune system in younger patients (Benchimol et al., 2011).
Finally, colorectal cancer (CRC) development is an important and potentially life-threatening complication of colitis. A recent study from Denmark, involving over 7000 UC patients from a large inception cohort, demonstrated CRC rates ranging from 3–8% after 40 years of disease duration (Söderlund et al., 2010). The risk was higher for males, with a relative risk compared to females of 1.6 (CI 1.2-2.2). An earlier review of this population suggested that the incidence of CRC may be declining when compared to historical rates, and that there was a clear reduction in mortality from CRC in the UC population. UC-associated CRC is more common in patients with a family history of colorectal cancer, in those with longer disease duration, and in those with concurrent primary sclerosing cholangitis (PSC) (Lakatos and Lakatos, 2008). Furthermore, histological inflammation and the degree of disease activity are also recognised as risk factors for CRC development in UC (Gupta et al., 2007). Importantly, many of these observations have only become clear through linkage studies involving well-defined, longitudinally observed IBD cohorts.

2.4.3 Can we modify the behaviour of IBD in 2011?

As presented previously, there is now some evidence to suggest IBD outcomes are changing. For example, observations suggest reduced surgical rates for UC, and also to a lesser extent, for CD (Vind et al., 2006). A number of factors predict that the behaviour of IBD should be evolving in 2011. Firstly, earlier diagnosis of IBD, due to improved symptom recognition and more sensitive investigations, has occurred. Significant advancements in IBD therapeutics have also taken place. Better treatment given at an earlier stage of the disease process should reduce disease activity, improve patient quality of life, avoiding complications and the need for surgery. The following paragraphs will briefly cover current therapy for IBD, some of the recent advances that have occurred, and their impact on disease evolution patterns.

2.4.4 Medical Management

There is currently no cure for IBD. Modern treatment goals focus firstly on inducing clinical remission, and then on maintaining this remission over the long term. Ultimately the aim of therapy is to achieve complete healing of all mucosal inflammation, as assessed both macroscopically and on a microscopic level. Strong evidence exists suggesting that achieving mucosal healing can change the behaviour of IBD, leading to reductions in disease related complications and improved quality of life (Rutgeerts et al., 2006). Before discussing specific therapeutic classes, it is worth considering some recent advances in IBD treatment principles.

Firstly is the concept of individualised treatment, with targeted therapeutic strategies based on the severity of the disease in the specific individual. This strategy relies on the ability to accurately identify those patients at highest risk of disease progression and serious complications, and targeting the most aggressive treatment in this group. Knowledge gained from sound longitudinal epidemiology research remains central to this treatment paradigm. The second important principle of management relates to maximising medication efficacy and adherence, minimising toxicity and treatment-related risk, and preventing hospitalisation, surgical interventions and associated
complications. With particular regard to paediatric patients, therapy needs to promote the maintenance of physical and psychosocial growth and development, and reduce disease related disability (Dubinsky, 2008). Finally, as with any complex, chronic medical condition, the management of IBD should occur in a strong, collaborative, multi-disciplinary framework.

**CD**

While medical therapy for CD has evolved extensively over the past 15 years, the evidence based therapeutic options in CD management are still relatively limited. Broadly speaking, treatment falls under medical or surgical approaches, and is largely determined by patient demographics, disease location, disease severity and the presence of complications. In practice, this involves a thorough clinical, biochemical and endoscopic assessment in all patients to allow an individualised approach to therapy.

Given the pathophysiological models previously described for IBD, it is not surprising that the cornerstone of IBD therapy is based on manipulation of the immune system or intestinal microbiota. The main classes of drugs used in treating CD include corticosteroids, the aminosalicylate or 5-aminosalicylic acid (5-ASA) compounds, antibiotics, immunomodulators, and the newer biological class of medications which specifically target cytokine pathways that are up-regulated in IBD.

**Corticosteroids**

A Cochrane review, revised in 2010, assessed the evidence for corticosteroids inducing remission in CD (Benchimol et al., 2008). The authors reviewed a total of 8 studies, 2 comparing steroid to placebo, and 6 comparing steroid to 5-ASA agents. Overall, steroids were found to be effective at inducing remission in over 80% of cases, with steroids also having a better efficacy than 5-ASA agents. However, while corticosteroids are widely used for the induction of clinical remission, they are unfavourable agents for long-term disease maintenance due to their unfavourable side-effect profile (Hanauer et al., 2005). There is also a lack of evidence regarding maintenance of remission or their ability to alter the disease progression of CD (Travis et al., 2006, Hanauer et al., 2005, Faubion et al., 2001).

**Aminosalicylates (5-ASA agents)**

Although these agents have previously been used extensively in CD, the evidence for the role of 5-ASA agents in CD is weak. A meta-analysis published in 2008 concluded there was only a very limited role for this class of therapy in CD management (Wong and Bressler, 2008). There is, however, some evidence to support the use of 5-ASA’s in a subset of patients with terminal ileal or colonic CD, with a more recent meta-analysis from 2011 suggesting a very slight benefit in regards to the induction of remission, but no clear benefit in the long term prevention of clinical relapses (Ford AC et al., 2011).
Similarly, there was no evidence for a significant disease modifying effect of 5-ASA compounds on CD behaviour.

**Antibiotics**

The antibiotics metronidazole and ciprofloxacin have been widely used in IBD treatment, despite the fact that their efficacy is largely unproven. A recent meta-analysis of controlled trials of antibiotics in CD, published in 2011, found a slight benefit for luminal CD in both the induction and maintenance of remission (Khan KJ, 2011). Antibiotic use for complications of CD, including local abscess formation, is common. Randomised clinical trial evidence exists for the short-term use of metronidazole to reduce recurrence post-operatively (Rutgeerts et al., 1995), and for ciprofloxacin used in combination with biological therapy in treating peri-anal fistulae (West RL, 2004).

**Immunomodulators**

A number of agents are included in this class. Azathioprine and 6-Mercaptupurine are thiopurines, and have been the most extensively studied in CD. Methotrexate has also been used widely. While they are slow to induce remission, thiopurines have been used for decades as maintenance therapy in more severe disease, or in those identified as high risk phenotypes that would be likely to progress (Sandborn W, 2000, Travis et al., 2006, Akobeng, 2008). Thiopurines have a complex metabolic pathway which is likely to be responsible for the wide individual variation in effectiveness, doses and tolerability demonstrated among patients (Bradford and Shih, 2011). While there is little long-term controlled data available for their effect on CD evolution, this is likely to reflect a lack of adequately designed longitudinal follow-up studies, rather that the ineffectiveness of these medications. In addition, the use of thiopurines later in the course of the illness may also reduce their efficacy (Akobeng, 2008). Data from Cosnes et al demonstrated no significant change in rates of surgery in patients taking Azathioprine, however most patients had been taking the drug for less than three months, and may have not achieved maximal dosage (Cosnes et al., 2005). In addition, the therapy may have been introduced late in the disease course when strictures had already occurred and the inflammatory burden was less.

**Biological agents**

Biological agents are the most recent addition to therapy in IBD, have dramatically changed the approach to modern CD management, and have demonstrated the ability to alter the behaviour and complications of disease. The two commercially available forms in Australia (infliximab and adalimumab) block the effects of the cytokine tumour necrosis factor-alpha (TNF-alpha), reducing the inflammatory response found in CD. They are both effective in luminal and peri-anal CD, with randomised controlled evidence for remission induction and maintenance. In the ACCENT 1 study, almost 60% of patients responded by week two to the first dose of infliximab, with longer term remission rates of 39% at week 30 (Hanauer et al., 2002). Similar responses have also been observed with adalimumab, with significant reductions in CDAI, reduced rates of steroid dependence, and
clinical remission (Sandborn et al., 2007). Evidence is also available for reduced surgical rates, improved fistulae healing, and reduced rates of hospitalisation (Feagan BG, 2008, Rutgeerts et al., 2006).

However, there are some barriers to the widespread use of biological agents. Firstly, these agents are expensive. Secondly, they require either intravenous or subcutaneous injection. Local and systemic reactions to these agents have been observed, secondary to the development of antibodies against the agents. Finally, safety concerns also exist, particularly regarding infection and malignancy risk. Long-term safety with biological use has been studied from the large, prospectively observed TREAT registry (Lichtenstein et al., 2006). This registry of over 6000 IBD patients treated with a biological agent suggested that the risk of serious infection was more likely related to concurrent steroid or narcotic use, rather than biologic use alone. These observations are another example of the use of registries in the study of disease related outcomes.

**UC**

Like CD, the treatment of UC is generally life-long. The principles are also similar, aimed at inducing clinical remission, healing of intestinal mucosa, and reducing the complications that occur from poorly controlled disease. Treatment is also tailored to the individual, with disease location and severity having a significant impact on the therapy applied.

**Proctitis and Distal colitis**

Topical applications of steroid and 5-ASA have an established role in the treatment of rectal disease, with controlled evidence supporting their effectiveness for the induction and maintenance of clinical remission. For example, remission rates from a large meta-analysis of up to 93% have been published (Marshall and Irvine, 1995). A more recent prospective trial published in 2000 randomised patients in clinical remission to maintenance 5-ASA or placebo suppositories. Relapse rates at 12 months of over 80% were observed in those receiving placebo, compared to 32% in the 5-ASA arm (Hanauer S et al., 2000). Direct comparisons between topical steroid and 5-ASA show better efficacy for 5-ASA agents (Gionchetti et al., 2004).

Topical therapy is also useful in distal colitis, although disease higher than the rectum generally requires enema therapy in addition to suppositories (Ng and Kamm, 2009). Studies also suggest that topical therapy is preferred over oral therapy in this group, with more rapid induction of remission (Ng and Kamm, 2009). For those patients who fail to respond to topical therapy, the addition of systemic 5-ASA therapy is required, with consideration for further therapeutic escalation including the use of corticosteroids and immunosuppressives.
Pancolitis

Systemic therapy with oral 5-ASA remains the treatment of choice for mild-moderate pancolitis, and can be considered as add-on treatment for distal disease not-responding to topical therapy. Patients who take an oral 5-ASA are almost 6 times more likely to experience a regression in the severity of disease, suggesting these agents may have a disease modifying effect (Picco et al., 2006). Up to 90% of patients can be maintained in remission with oral 5-ASA therapy, however compliance rates in long term therapy are as low as 40% (Kamm et al., 2008). More severe 5-ASA refractory disease generally requires corticosteroids for remission induction, followed by maintenance therapy with immunomodulators to prevent relapse (Ng and Kamm, 2009). Although there is little long term controlled data in this area, a recent pooled analysis of placebo-controlled trials of 6-Mercaptopurine and Azathioprine demonstrated a significantly reduced risk of UC disease relapse with their long-term use (OR 0.41) (Timmer et al., 2007).

Severe, fulminant UC requires inpatient care, and carries a significant risk of colectomy. Intravenous steroids are generally effective, however in those failing to respond, salvage therapy with either cyclosporine or Infliximab have been used (Ng and Kamm, 2009, Burger and Travis, 2011). These agents may avoid the need for colectomy in up to 50% of cases. The use of salvage agents is particularly useful in the setting of new onset colitis, where patient acceptance of urgent colectomy is generally lower than in those with long-term, chronic disease.

2.4.5 Surgical Management

CD

Historical data suggests that patients with CD have a high risk of requiring surgical intervention at some stage in their disease course, with cumulative surgical rates of 44%, 61% and 71% at 1, 5 and 10 years after diagnosis (Bernell O et al., 2000, Mekhjian HS et al., 1979). Common indications are for perforating and stricturing disease phenotypes. Unfortunately, surgery does not provide a cure in the setting of CD, with recurrence of CD in the post-operative setting almost universal. Research has shown endoscopically proven disease visible in 73% of patients within 1 year of surgery (Rutgeerts P et al., 1990). Re-operation rates of over 50% have been documented (Fichera et al., 2006).

UC

As opposed to surgery for CD, surgical intervention for UC, in the form of removal of the entire colon and rectum, is an essentially curative procedure. Colectomy rates vary between studies, ranging from 8.7 – 54% 10 years from diagnosis (Hoie et al., 2007). A recent UK based study revealed a colectomy rate as high as 23% just 1 year after diagnosis in their local population (Ho et al., 2006).

Surgery for UC is not without morbidity and mortality risk, and is generally reserved for patients who fail to respond to intensive medical therapy, or those who develop complications of UC including
high grade dysplasia or cancer (Frizelle and Burt, 2001). It should be remembered, however, that colectomy with subsequent restorative ileoanal pouch surgery can provide reasonable bowel function without stoma in the majority of operated patients, and surgical consultation should occur early in severe disease (Frizelle and Burt, 2001). Local Australian population-based data examining surgical rates for UC are currently lacking.

2.4.6 Quality of life in IBD

While clinicians typically measure the direct impact of disease on their patients, for instance changes in laboratory tests or imaging, it is important to consider the impact that IBD has with respect to quality of life. Assessing health-related quality of life (HRQoL) takes into account all aspects of a patient’s life, including psychological and functional domains that may be impacted upon by a specific disease. IBD is associated with particularly distressing symptoms including the need for frequent bowel actions, abdominal pain, fatigue, sleep disturbance and poor nutrition. The impact of IBD on HRQoL is also likely to be significant due to IBD being a chronic, relapsing condition with the diagnosis often occurring at a young, developmentally important age. All of these can adversely influence HRQoL indicators, a fact which has been recognised for over 20 years (Sorensen et al., 1987).

An appreciation of the impact of IBD on HRQoL is crucial for clinicians, and is also an important measure of efficacy in IBD therapeutic outcome studies and disease evolution observations. HRQoL also has a direct impact on health-related economic costs. Changes in quality of life can be longitudinally assessed in IBD population cohorts, with several previous publications revealing significant variations in HRQoL measures that closely relate to changes in disease activity (Andrews et al., 2010). For example, CD activity levels have been shown to be directly associated with HRQoL measures, with improved well-being documented in those patients who are in clinical remission (Feagan et al., 2007).

A number of general and IBD-specific questionnaires have been developed to assess HRQoL in IBD patients, and will be elaborated on in the following sections.

36-item Short-Form General Health Survey

The Medical Outcomes Study 36-item Short-Form General Health Survey, or MOS SF-36, is an example of a general scale to assess HRQoL. The 36 questions evaluate limitations in physical, social, psychological and functional domains. It is a non-specific questionnaire suitable for assessing HRQoL in many chronic diseases, and has been applied extensively to IBD cohorts (Ware and Sherbourne, 1992). The quality and reliability of the SF-36 has been previously tested across a diverse range of medical conditions (McHorney, 1994). A number of IBD studies have used the SF-36 as an outcome
marker (Miehler et al., 2008, BORGAONKAR and IRVINE, 2000). The complexity and length of the tool, and time required for completion, has lead to the development of shorter, IBD-specific HRQoL tools.

**IBDQ/SIBDQ**

The Inflammatory Bowel Disease Questionnaire (IBDQ), developed by McMaster University in Canada, is a useful and validated disease-specific HRQoL assessment tool applicable to patients with IBD (Guyatt et al., 1989). Areas covered in the questionnaire include bowel related symptoms, general symptoms, emotional function and social function. However, due to the length of the full IBDQ (32 questions), a shorter version, which is easier to apply, has been trialled. The short version (SIBDQ) is limited to 10 questions. Irvine et al have demonstrated that the SIBDQ has clinical validity, with a close correlation between the SIBDQ and the full IBDQ in CD patients (Irvine et al., 1996).

### 2.5 IBD POPULATION-BASED REGISTRY

In general terms, clinical registries involve the collection and subsequent analysis of information relating to a specific disease. They can take many forms, ranging from administrative registries through to those designed specifically for longitudinal study (Gladman and Menter, 2005). This discussion will focus on clinical registries and clinical quality registries, being most relevant to the study of chronic diseases such as IBD. The benefits of these types of registry relate to both their ability to monitor outcomes of patients with chronic disease, and to ultimately optimize quality of care (Evans and al, 2011).

A high quality registry aims to collect standardised information on all patients with a particular condition, and may be hospital or community-based. Community-based clinical registries have the added benefit of eliminating the referral bias inherent to hospital-based registry programs. Clear operating principles and technical standards for the implementation of Australian population-based clinical registries have been recently suggested through the National Quality and Safety Health Services Standards.

#### 2.5.1 Clinical Registries; Background and Rationale for use

Systematic collection of data on health outcomes is fundamental to the successful long-term implementation of healthcare (Evans and al, 2011). Without such data collection and analysis, health care providers, and ultimately governments, risk spending money on potentially expensive care with no definable endpoints or goals (Safavi et al., 2010). This is not a sustainable model for health care
resource allocation or delivery. The information derived from a well-designed registry is central to successful and streamline health-care planning, allowing disease outcome observations and subsequently standard-of-care benchmarking (Evans et al., 2011).

In recent years, there has been a rise in the formation and use of large-scale and methodologically robust clinical registries in Australia. This has largely been through the guidance of the Australian Commission on Safety and Quality in Healthcare (ACSQHC). This body, in collaboration with major healthcare stakeholders including the Monash University Centre of Research Excellence in Patient Safety and the National E-Health Transition Authority (NEHTA), have recently provided useful guidelines for the successful implementation and running of quality clinical registries. International standards on registry formation have also been published, including the recently released US-based guide to patient outcome-related registry formation (Gliklich and Dreyer, 2010).

There is strong emerging local evidence to support an expanding role for clinical quality registries in Australia. The example of the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) clearly demonstrates the potential benefits derived from registry formation. The AOANJRR, established in 1999, has been central to identifying problems with specific joint prostheses (Graves and al, 2004). Recently, longitudinal observations from the registry suggested poorer outcomes relating to a specific hip prosthetic device, eventually leading to its withdrawal from the Australian market in 2010 (Prosser and al, 2010). It is estimated that $80 million per year will now be saved, due to the projected reduction in need for surgical revision procedures from prosthetic failures.

There are no true population-based IBD registries in Australia. A number of small IBD databases exist, mainly in hospital settings, however there are no large-scale, population-wide registries currently operating. As described previously, IBD is a complex, chronic disease, predominantly affecting young patients, and is associated with significant health-care associated costs. These attributes make IBD suitable for study through a population-based registry, a need that is currently unmet within Australia.

2.5.2 Structure and planning in Registry establishment

Registry purpose

When planning the structure of a clinical registry it is first important to consider what purpose the registry will achieve for each specific situation. For example, if disease outcomes and complications are to be reviewed, then the structure of the registry needs to be extensive enough to allow ongoing real-time reporting and collection of data relating to the relevant clinical events. If the registry is aimed at simply providing an up to date and comprehensive record of all patients in a region with a
particular illness, then a more limited data set can be considered. For example, only identifying demographic data and contact details may need to be recorded and maintained.

**Data sources and composition**

The potential sources of the data that contribute to a clinical registry are diverse. Data may be extracted from existing electronic databases, such as radiological or pathological databases. Alternatively, information for a registry may be prospectively and purposefully collected from medical records or from clinical staff involved in treating patients with the condition in question. While the latter method is more time consuming and labour intensive, it is probably the preferred method as it is less prone to bias from incorrect coding or initial documentation.

The key features of the initial data collection include limiting collected information to a core, reliably reproducible, set of elements (Evans et al, 2011). This should include data to confidently identify and follow patients prospectively. It can also include factors specific to the illness in question, for example the date and type of procedure performed for a cardiac device registry, or the date and location of fractures for an osteoporotic registry. Ideally, data should be objective and not subjective, the former being less prone to interpretation error.

Clinician involvement is crucial to maintaining the quality and relevance of the data collected. This can be labour intensive, and is not open to financial remuneration. Linking clinician involvement in registries with medical accreditation and professional development activities recognised by their respective governing societies may be one way of improving participation. Another option to improve registry up-take is to incorporate registry involvement when establishing business models for public or private practice, and within patient billing structures. A recent article published in The Asia-Pacific Journal of Public Health in relation to establishing a pilot coronary syndrome registry in Egypt, highlighted the importance of clinician involvement (Safavi et al., 2010). It reflects on the need to build a culture of applied research among clinicians in general, to outline and emphasize the importance of their own involvement in basic clinical epidemiology and registry maintenance, and how this involvement can be linked to improving quality and cost-efficiency of care. This same group also conclude that the main constraints to effective registry formation found relate to inadequate human resources and technical infrastructure.

The population at risk of the condition should be accurately defined, and efforts made to maximise case ascertainment rates (Evans et al., 2011). Data is then generally pooled in a central location. While previous paper based registers predominated, it has been suggested that registries are maintained electronically, either on institutional hardware or internet based, offering easier data collection, more secure and reliable storage, and easier analysis (Evans et al., 2011, Gladman and Menter, 2005).
Depending on the level of clinical and demographic details held within this databank, registers can then be interrogated for a number of purposes. These may include maintaining disease incidence and prevalence rate figures, documenting disease-related behavioural observations, or the assessment of patient outcomes against accepted standard of care benchmarks. This last point is important, as it highlights a difference between the two commonest forms of registries in practice. While the clinical register only needs to retain simple demographic and diagnostic data, the clinical quality register requires more extensive data input to allow useful longitudinal observations.

In broad terms, clinical registers are simple databases that aim to systematically collect health-related information specific to particular treatments, interventions, or illness, from a defined population. An example of this would be the continuous recording of basic information of all patients treated for cerebrovascular accident (CVA), through either a single hospital based stroke unit or in a defined non-hospital community based population. These clinical registers aim to provide epidemiologically robust data on measures such as disease incidence, and may form the basis for future research based on the additional interrogation of registry participants to answer specific questions.

Conversely, clinical quality registers are more complex in their design and structure. They aim to collect more extensive data related to outcomes and treatments. This in turn allows the generation of progress reports, providing the opportunity to improve in health care quality and delivery. Inherent in their more complex nature, clinical quality registries tend to have higher associated establishment and running costs (Evans et al, 2011). Examples of current clinical quality registers operating successfully in Australia include the Australian Cardiac Procedures Registry (ACPR), the previously described Australian Orthopaedic Association’s National Joint Replacement Registry (AOA NJRR), and The Australian Motor Neurone Disease registry. These registry models are appropriate to consider when planning for a population-based IBD registry.

**Consent issues**

Contribution to registries should be informed and voluntary, and should be offered to all eligible patients. Consent can generally take two forms, either opt-in or opt-out (Singleton and Wadsworth, 2006). Opt-out consent relies on the ethical principal of presumed consent. The process of opt-out consent involves the provision of an explanatory statement to potential registry participants outlining the principal of the registry, its aims, and what personal and clinical information will be kept. Clear contact details of the registry governing body should be provided, in addition to details on where the data is maintained, and how the personal information may be used in the future. This form of consent must still be voluntary, adequately informed, and provide mechanisms for withdrawal at any stage.
Opt-in consent involves individual patients being personally approached by registry staff, usually supplying both verbal and written information pertaining to the registry. Based on this discussion, the participant then signs a consent form allowing their inclusion in the registry. This process is significantly more labour intensive than the opt-out model. Some argue that opt-in consent is more ethically sound than the opt-out method, as it does not simply rely on patient inertia for presumed consent (Sommerville, 2001). However, this method may also be more open to researcher-driven manipulation and coercion, and has been associated with retention rates as low as 40-50% described in some registries (Evans et al., 2011).

There is strong precedent in Australia when choosing the model of consent for a new clinical registry, with approximately 75% of local registries currently employing opt-out consent. However, as of 2010 the National Health Medical Research Council (NHMRC) has not yet produced a position statement with regard to opt-out consent, which still leaves individual Human Research Ethics Committee’s (HREC) from different institutions in a challenging position when considering new registry applications using this form of consent.

**Registry maintenance**

Registry maintenance, including governance, should ideally be undertaken by a group independent from those who actually provide the health care. In addition, rigorous internal quality control mechanisms should exist including reviewing how cases are identified and defined to be included in the registry, which variables are to be collected on participants, and cross-referencing to ensure reliability and accuracy of the stored data (Bufalino et al., 2011). Formal processes need to exist regarding access to, and reporting of, data. Routine and independent quality assurance routines should be established.

Whatever the format of the registry, data security is another critical consideration. The collection of personal identifying details, central to ability to follow patient outcomes in the long-term, obligates the clinicians overseeing this data to stringently consider privacy. In Australia, working within the Australian code for the responsible conduct of research is strongly recommended, as is consultation with the National statement on ethical conduct in human research. Registries should be maintained in an environment with extensive experience in handling confidential information, such as a hospital or established research foundation. Consideration of patient privacy is thus central to new registry development, and legislation relating to privacy laws is currently under senate review.

**Financial considerations**

Although the data derived from high quality registries can provide valuable insights into disease-related outcomes, there are extensive costs associated with their establishment and maintenance (Bufalino et al., 2011). Therefore, financial resourcing is an important consideration when planning a
clinical registry. From the time of registry conception it is crucial to have financial provisions to cover costs associated with adequate data collection, storage, reporting and quality control activities.

Costs to consider include those relating to IT support for database establishment and ongoing management. Expenses incurred in relation to hardware and software maintenance, and data security should also be considered. Central to successful implementation of a useful clinical registry is the provision of funds for adequate staffing, allowing for quality data collection, data entry, regular updating of registry details, rigorous data quality control, database interrogation and the generation and dissemination of reports. Further costs relating to data linkage queries may also need to be considered in some situations (Bufalino et al., 2011).

Before applying for funding, it is useful to attempt to demonstrate that the registry will have a positive cost-benefit impact on care related costs, in addition to improving quality of patient care (Bufalino et al., 2011). The example of the success of the National Joint Replacement Registry has already been discussed, however proving cost effectiveness can sometimes be challenging. The possible financial benefits are often secondary, delayed, and more difficult to demonstrate. Registry outcome data may gradually feed back to clinicians, eventually allowing streamlining of care or improved targeting of therapies to those patients who will gain most benefit.

Registry funding options can come from a variety of sources, from both within the private and public sectors. These include, but are not limited to, departmental budgets from individual hospital or research foundations, healthcare industry sponsorship including pharmaceutical companies, medical device manufacturers and health insurance agencies, and research grants from federally funded sources including the NHMRC and the Australian Commission on Safety and Quality in Healthcare (ACSQH). Whatever the source of funding, careful consideration needs to be given to issues such as data ownership and utilisation. This is required to prevent the unethical use of registry information, particularly in the case of private industry-related sponsorship. There is a wide mix of funding types currently supporting large scale Australian registries, and there is a strong argument to be made for central regulation and formal guidelines under the umbrella of a National policy framework to govern this area of registry design.

One potential way of reducing costs associated with registry maintenance is to evolve methods for accurate and high quality data collection automatically from already collected data-sets (Evans et al, 2011), however issues relating to privacy and technological constraints need to be resolved.
2.6 CONCLUSION

The advances in knowledge regarding IBD since the first description of the disease almost 100 years ago have been significant. Clinicians have a host of sophisticated diagnostic tools and treatment options to investigate and treat patients with IBD. However, despite these advances, the true cause of IBD remains unknown, and no cure exists. Unexplained changes in incidence rates are still being observed around the world. New insights into microbial, environmental and genetic influences in disease onset, as well as factors contributing to disease progression, are rapidly emerging. The impact of new therapies is also becoming clearer. Despite these advancements, the disease still has a severe and disabling course in many patients, particularly those in the prime of life.

In 2010, the World Gastroenterology Organization (WGO) marked World Digestive Health Day (WDHD) by convening an international meeting of leading IBD clinicians and researchers from around the world. This allowed a unique global summary of current IBD understanding from Europe, North America, South America, South East Asia, and Australasia. With the dramatic changes in IBD incidence and behaviour that has evolved in recent time, and between different geographical areas, the taskforce identified access to ongoing reliable epidemiology data as one of the leading areas of need with regard to research related to IBD worldwide (Baumgart et al., 2011). Specifically, population-based research focusing on registry establishment was highlighted.

With these points in mind, this research thesis has been designed to attempt to answer a number of questions at the core of our evolving understanding of IBD epidemiology. Foremost, a current, accurate population-wide assessment of local IBD incidence rates will be made. A direct comparison with incidence figures derived from the same population in 2007 will allow an assessment of whether local IBD incidence rates have changed over time. Secondly, unique Australian population-wide IBD prevalence rates will be calculated. Thirdly, all new cases identified in the incidence project will be incorporated into a pilot IBD registry. This unique, pilot Australian population-based IBD registry will provide the basis for an inception cohort, which, through careful longitudinal observations, will yield unique insights into early disease course and behaviour in an Australian community setting. Future studies of this cohort will provide data on many other areas relating to IBD including local health-economic assessments, health resource utilization rates, IBD-related disability assessment, and the recognition of possible environmental and genetic influences relating to IBD pathogenesis.
CHAPTER 3.

RESEARCH DESIGN.

Chapter 3 provides an outline of the methodology chosen for this research project. It also includes the rationale behind the research design for each different aspect of the project, supported by reference to current IBD epidemiology literature. Section 3.1 will present an overview of issues relevant to population-based epidemiology studies. Sections 3.2, 3.3, 3.4 and 3.5 define specific methodology choices for the main components of this research, namely the calculation of population-wide IBD incidence rates, prevalence rates, and the establishment of a pilot population-based IBD registry. Section 3.6 reflects on possible errors and difficulties associated with the methodology chosen, the potential impact of these errors, and steps taken to minimise them.

3.1 STUDY DESIGN.

Experimental studies, such as randomised controlled trials, involve manipulation of the variables to allow clearer determination of cause and effect. In contrast, epidemiological research is observational, with central concepts including measurement of disease frequency, risk factors or exposures, and outcome measures (de Courten et al, 2007). Observational studies do not involve any manipulation of the variables involved, as they usually occur in real world settings as opposed to the controlled environment of a clinical trial. Ecological, cross-sectional, case-control and population-cohort studies are all usually observational in nature.

The design of this research project was the result of three stages of planning. Firstly, it was important to define the principal aims of the research. This was achieved by collaborating with senior researchers and clinicians, both at St Vincent’s Hospital, Melbourne, and within the study population region of Barwon. This process led to three primary aims of the research being defined. Firstly we aimed to prospectively establish the incidence and prevalence rates of IBD within the Barwon region. We also aimed to create a pilot population-based registry based of newly diagnosed incident IBD cases identified, to allow longitudinal disease evolution and behaviour assessment.

The second phase involved specific consultation with academic supervisors, with a particular focus on current best-practice descriptive epidemiological methods. Professor John McNeil, from the Department of Epidemiology and Preventive Medicine at Monash University, was central to this aspect of the project, and his advice regarding appropriate methodology for this research during the early consultative phases was invaluable. Further regional-specific epidemiology methodological advice was obtained from Associate Professor Julie Pascoe, head of department at the Epidemiology and Biostatistics Unit of Barwon Health.
The third and final phase of research methodology planning involved a systematic literature review, a summary of which has been previously outlined in Chapter 2 of this thesis. The strengths and weaknesses of different studies involving descriptive IBD epidemiology were critically assessed, with a particular focus on more contemporary studies from our local region and internationally.

The key design features chosen for each aspect of this research are thus summarised in Table 3.1 below.

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<th>Chapter 4</th>
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<td>Prospective case ascertainment</td>
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<td>12 month study period July 1(^{st}) 2010 until June 30(^{th}) 2011</td>
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<td>Capture-recapture methodology, multiple case sources</td>
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<td>Identifiable data captured allowing rigorous clinical confirmation of cases</td>
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<td>Incident rate calculations including crude rates and WHO age standardised rates</td>
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<td>Comparison with previously defined loco-regional IBD incidence rates from same population</td>
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<th>IBD Prevalence rate study</th>
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<td>Capture-recapture methodology, expanded further into the primary care setting (GP clinics)</td>
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<td>Identifiable and non-identifiable data captured, allowing partial clinical confirmation of cases</td>
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<td>Recording of basic demographic and disease-related information</td>
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<td>Prevalence rate calculations including crude rates and WHO age standardised rates</td>
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<td>Prospective case capturing</td>
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<td>All newly identified incident IBD cases included</td>
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<td>Opt-out consent process</td>
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<td>Epidemiologically sound identifiable demographic and core disease-specific details recorded</td>
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<td>Manual case capture and data entry</td>
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<td>Registry maintained on a secure, password protected computer in Excel format</td>
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*Table 3.1 Study design overview.*
The incidence and prevalence studies in this thesis were observational in nature. The disease registry formation involved the establishment of an inception cohort. However, for the purpose of this thesis, the registry was designed only as a pilot project to assess the feasibility and clinical validity of establishing an IBD population-based registry in this region. While time restrictions related to completing a research higher degree precluded long-term observations from this new inception cohort, the registry will, however, provide the platform for valuable longitudinal disease-specific observational research into the future. Interim disease evolution observations are presented in Chapter 6 of this thesis.

The final design of the methodology for this current project was also closely matched to that used in the previously undertaken study of IBD incidence in this region from 2007 described elsewhere (Wilson et al., 2010). This was done to allow valid clinical comparisons between the two patient inception cohorts and IBD incidence rate calculations.

3.2 IBD INCIDENCE RATE STUDY.

To accurately define and characterise disease frequency rates, consideration needed to be given both to the accuracy of IBD diagnosis, and to carefully define the at-risk population in which IBD was to be studied. Without this, the validity of any final rate estimations would have been significantly reduced.

3.2.1 Diagnostic accuracy.

As no single test was available to diagnose IBD, consideration was made to a set of specific diagnostic criteria to accurately confirm the diagnosis of new IBD cases. These were based on diagnostic definitions used in other large-scale, population-based observational IBD studies, details of which have been described previously in Chapter 2 (Wilson et al., 2010, Burisch et al., 2011). The full diagnostic criteria chosen for this research are presented in Chapter 4, section 4.3.2.

3.2.2 Population definition.

Accurately defining the population at-risk of developing IBD in this area was crucial. The Barwon region was chosen due to a number of attributes which are suited to high quality epidemiological research.

Firstly, it is clearly defined in terms of geography. The study boundaries, as illustrated in figure 3.1, are accurately defined by the Barwon Statistical Division (BSD), details of which can be found on the Australian Bureau of Statistics (ABS) website (www.abs.gov.au). A Statistical Division (SD) is an Australian Standard Geographical Classification (ASGC), representing a clearly defined geographical region. SD’s are maintained by the ABS for the purpose of collecting and disseminating reliable
geographically-defined statistics, and are based around sets of defined postcodes. Population records are accurately maintained from the Australian Census data, a nation-wide compulsory population assessment which occurs every 5 years.

Figure 3.1 Location of study population (permission granted for illustration by Dr J Wilson (Wilson et al., 2010)).

The Barwon SD sits 75km to 150km South-West of Melbourne in Victoria, Australia. The land size is approximately 9000 square kilometres. The economic and population centre of the Barwon SD is the city of Geelong, the second largest city in Victoria, and is located at latitude 38°S. The most recent total population estimate for the study region in 2011 is 293,426 (source G21 and ABS population estimates). This compares with the Victorian state population estimate of 5,585,600, and the total Australian population estimates from the same time of 22,477,400 (www.abs.gov.au). Thus, the study area represented 5.3% and 1.3% of the total Victorian and Australian population, respectively. Comparative demographic details are presented in table 3.2 below.
When attempting to extrapolate and compare local results with the broader Australian community or previously published international results, it is important to consider possible differences between the populations. While the local population characteristics are largely comparable with the national data, some differences are worth noting. The percentage of Indigenous Australians in Barwon is less than the national figure. More residents in Barwon were born locally. The unemployment rate in Barwon is slightly higher than the national figure, and there are less people employed in professional occupations. Finally, there is a suggestion the population may be slightly older, with the proportion of the inhabitants over 65 above the national average. Further comparisons between the study population and the expected internationally accepted WHO age-standardised population are presented in Chapter 4.

Geographically, the Barwon region includes a range of urban, rural and coastal zones, and has a temperate climate. Local industry focuses on farming, mining, business and tourism. Migration rates into and out of the Barwon SD are relatively stable (G21 website). The region maintains an independent infrastructure of healthcare-resources based in Geelong, the only city in the catchment area. There are a limited number of public and private hospitals in operation, an active General Practice network, and extensive secondary health services including pathology, medical imaging facilities, and pharmacy resources. These features favour maximisation of case ascertainment rates, as the majority of the population in the region are able to access comprehensive healthcare locally. A dedicated group of local specialist and general clinicians were available to prospectively identify potential IBD cases from within the community on a regular basis.
Barwon Health and The Geelong Hospital have an active Epidemiology and Biostatistics Unit which has published widely in the past with regard to the epidemiology of a number of chronic diseases. In particular, extensive population-based research has focused on osteoporosis, in the form of internationally recognized Geelong Osteoporosis Study, involving ongoing, prospective determination of the local burden of disease, and identification of novel risk factors for the development of osteoporosis and subsequent fractures (Pasco et al., 2011). Previous IBD-specific research has also been completed locally, with discovery of high levels of IBD in a prospective incidence study from 2007 (Wilson et al., 2010).

All of these population features combine to make the Barwon region appropriate for the accurate assessment of IBD incidence rates.

3.2.3 Time frame.
A population-based determination of IBD incidence over a 1 year period was chosen. This length of study was deemed sufficient based on previous local and international research assessing population epidemiological data.

3.2.4 Capture-recapture methodology.
Unlike a hospital based IBD study, community centred research has no central database from which to capture and collect details of information about potential new cases. Determination of IBD incidence rates therefore involved collection of data from a variety of potential sources. This capture-recapture methodology aimed to maximise case ascertainment rates, validating the subsequent disease frequency estimations. Details of the data sources are discussed in further detail under the methodology headings in Chapters 4.

3.2.5 Data elements and planned calculations.
Identifiable demographic data were first collected from local clinicians. This allowed the PI to comprehensively and longitudinally review the complete demographic and clinical data available on each potential case. This occurred through review of medical records, correspondence, and relevant investigation results. No direct patient contact was made by the PI during this process. Once confirmed as an incident case of IBD, specific data regarding IBD phenotype and disease extent at diagnosis were then recorded. Details on presenting symptoms, risk factors, hospitalisation, surgery and therapy were also recorded. Details of the data collected are outlined in the ‘IBD Incident Case Proforma’, presented in Appendix 1. Case confirmation three months after initial referral was made, and any disease-related events or treatments were recorded. Details are outlined in the ‘Three months from diagnosis – Review’ proforma in Appendix 2.
For the purpose of the incidence rate calculation, de-identified demographic details, including initials, gender, name and DOB, were ultimately retained. Data was stored in an Excel database held on a secure, password protected computer. This allowed for accurate estimations of crude IBD incidence rates, disease phenotype-specific rates, and of rates corrected for age and gender, while protecting patient confidentiality and privacy. Detailed results from this study could then be directly compared with comparable historical data published by Wilson et al from the same population studied in 2007/08 (Wilson et al., 2010).

### 3.3 IBD PREVALENCE STUDY.

The epidemiological concepts related to the estimation of local IBD incidence rates, described previously, are also applicable to the prevalence rate estimation component of this research. There are, however, a few key differences, as outlined in the following sections.

#### 3.3.1 Diagnostic Accuracy.

IBD cases that were initially identified from the incidence study but were found to be diagnosed before the study period were included in the prevalence study. These cases had clinical case confirmation by the PI, with diagnostic accuracy. However, as will be further discussed in section 3.3.5, due to the de-identified nature of the information obtained for a number of prevalent cases, there was no opportunity for retrospective diagnostic validation of each case. The validity and accuracy of IBD case confirmation for these patients relied on the referring doctor.

#### 3.3.2 Population definition.

The population used for the determination of the IBD prevalence rates was the Barwon Statistical Division, boundaries and details of which have been described previously in section 3.2.2.

#### 3.3.3 Time period.

A population-based determination of IBD incidence over a 1 year period was chosen. This length of study was deemed sufficient based on previous international epidemiological studies.

#### 3.3.4 Capture-recapture methodology.

When considering estimation of population prevalence rates, it was deemed necessary to further expand on the capture-recapture methods employed for the incidence rate estimation section of this research. The key difference focussed on greater involvement of local General Practitioners (GPs). This decision was based on the assumption that newly diagnosed incident cases of IBD would be most likely to require a higher level of care, including hospitalisation, endoscopic procedures and histopathological analysis, and would therefore be captured in the level of capture-recapture.
described for this group of patients. However, it was assumed that prevalent IBD cases may be clinically well and in remission during the study period, and therefore would not require procedures, hospitalisation or even specialist gastroenterology review that would allow case captured in the methodology described. This would have resulted in underestimation of true prevalence rates.

The local GP workforce was engaged in the research through a number of mechanisms, primarily through the local Geelong GP Association (GPA). A list of 280 GPs working across the region was generated through the assistance of the GPA. GP contact was maintained in a number of ways, including individual phone calls, regular publications in the local GP bulletin, and direct emails to all GPs listed within the division. In addition to GPs, the clerical practice managers of practices were also approached to facilitate case referral. Several educational activities were undertaken by the PI to engage local GPs and to raise the profile of the study and encourage patient referral. Finally, the PI attended a number of GP practices and assisted in IBD-specific data extraction.

3.3.5 Data elements and planned calculations.

There were some differences in the data collected for prevalence estimation compared to that collected in the incidence estimation study. Importantly, due to privacy and ethics constraints, only de-identified information was sought. Some demographic details, such as gender, age or date of birth, were requested, allowing the PI to cross-reference cases to ensure that the same patient was not included twice from different sources. Data on disease type, phenotype and duration were requested from the referring clinician. By retaining details of case source clinicians, it was also possible to establish which IBD patients were captured through mainstream gastroenterology specialty services, and which patients only had GP contact regarding the ongoing management of their disease during the study period.

3.4 PILOT POPULATION BASED IBD REGISTRY.

IBD is a chronic condition, generally following a course defined by exacerbations and periods of remission (Loftus et al., 2002). Study of the disease evolution of IBD is crucial to furthering our understanding of disease progression. The best way to observe this is in a prospective manner in a population-based setting, with an IBD-specific registry an excellent model on which to base such longitudinal disease observations.

The hypothesis for this section of the research was that it would be possible to establish a true population-based pilot IBD registry, based on all prospectively identified and clinically validated new cases of IBD from the region. This component of the research was closely linked to the IBD incidence estimation study. All clinically validated incident IBD cases were considered for inclusion in the pilot registry. The process of opt-out consent was used, with a letter of invitation being sent to all
potential patients. A copy of the consent form can be found in Appendix 4. After the letter had been sent, the case was automatically enrolled in the registry, on the basis of presumed consent. The format chosen for the pilot registry was an Excel database, located on a secure, password protected computer. Data entry was performed only by the PI, with data derived from paper-based case information, in addition to linkage with the previously described incident case cohort database.

For the registry to be clinically useful with regards to future prospective longitudinal study, simple epidemiologically-sound demographic elements were recorded. These included patient name, date of birth, gender, Medicare number, address and telephone number. The treating clinician and GP’s details were also recorded. This dataset would allow future contact with both the patient and treating doctor to assess issues such as disease progression, complications, medication and health resource use, quality of life impact, and assessment of the degree of disability associated with their disease. Furthermore, the rigorous documentation of phenotypic information at baseline would also allow for future identification of individuals who had a more complicated and serious disease course over time. Finally, through recall of lifestyle factors and childhood events, possible aetiological associations may be revealed. Further descriptions of formation of the pilot registry are found in Chapter 6.

3.5 SOURCES OF ERROR.

Errors may occur in any study design. Epidemiological observational research has its own unique error sources that need to be identified, and the impact of these minimized where possible. Thus, the potential impact of error is an important factor to consider when examining the results of such studies.

Most sources of error are addressed by considering the internal and external validity of a study (Introduction to clinical research handbook Monash University 2007). Validity refers to whether the study results are an accurate reflection of the actual facts. Internal validity refers to whether the study methodology is sound and therefore if the results will be true, or accurate. Internal validity is affected by misclassification, selection bias and inappropriate choice of measurements.

Misclassification is important in considering IBD incidence estimations. Firstly, it is critical to correctly identify cases as being true incident IBD cases, and to separate them from other conditions that may mimic IBD. Cases included in the incidence rate study were subjected to strict, rigorous and previously validated IBD diagnostic criteria. This reduced the rates of misclassification as a potential source of error, as did the method of revalidating cases after a further 3-6 months to ensure they still fulfilled these diagnostic guidelines. However, despite adhering to this, it is still possible some cases of IBD may have been incorrectly diagnosed, hence leading to a potential over-estimation of the final incidence. Conversely, true IBD cases that were in the early stages of disease and did not yet fulfil all the diagnostic criteria used for case confirmation, would have been excluded from the study. This may have led to an under-estimation of incidence rates. The case validity in the prevalence study was less robust for some cases. This was due to restrictions regarding data access relating to privacy and consent issues. The accuracy and quality of the data on a proportion of
prevalent cases relied entirely on the referring clinician, introducing greater potential for error with regard to misclassification of cases in the prevalence study.

Issues relating to the impact of case ascertainment need to be considered. Despite the capture-recapture methodology used, it is possible that some new IBD cases may have travelled outside the study area to seek medical assistance and have the diagnosis of IBD made. This source of error may have biased the final results, resulting in an under-estimation of incidence rates. However, a number of factors were considered to minimise the potential impact of this. The geographic isolation of the study population was one such factor. The fact that primary, secondary and tertiary level health-care services were available within the study area reduces the potential need for patients from this area being required to travel to another area for health-care. Finally, a previously undertaken survey of all GP’s working in the BSD revealed that the pattern of referral of potential new IBD cases would be to services located within the district (Wilson et al., 2010).

External validity refers to how well the results of a study in a specific population could be extrapolated to another separate population (Introduction to clinical research handbook Monash University 2007). It is important to consider what differences may exist between these two populations.

In the IBD incidence study (Chapter 4) and prevalence study (Chapter 5) it was important to compare the Barwon population to the broader Australian population, as significant differences between these two populations would have limited the ability to extrapolate disease rates nationally. Due to accurate and regular updates from the Australian Census collections, demographic factors such as age, gender, ethnicity and socioeconomics could be measured and compared. Table 3-2 compares features of the two populations, revealing that they were in fact highly comparable. The main difference observed related to lower rates of indigenous residents, lower rates of inhabitant who were born overseas, however the absolute impact of these differences is likely to be minor.

Another factor to consider when assessing the validity of extrapolation of local results to the broader Australian population relates to the physical location of the study population. Although the evidence remains inconclusive, previous reports on the impact of longitude and latitude on IBD epidemiology needs to be considered when applying locally generated disease frequency estimations to the broader Australian community (Wolters et al., 2007). The impact of potential sources of error will be further discussed in each individual chapter.
CHAPTER 4.

IBD INCIDENCE RATE ESTIMATION; RESULTS OF A PROSPECTIVE POPULATION-BASED IBD INCIDENCE STUDY.

This chapter summarizes the hypotheses, aims, methods, results and discussion related to the prospective, population-wide IBD incidence rate assessment in Barwon, Victoria.

4.1 BACKGROUND STATEMENT

IBD is a chronic, progressive and destructive gastrointestinal disease that is associated with significant morbidity and reduced quality of life (Engal and Neurath, 2010). It is generally accepted that health-related expenditure for IBD is high (Silverstein et al., 1999). Unexplained variations in IBD epidemiology have been observed, particularly over the last 50 years. From the late 1970’s, a steady increase in IBD incidence has been demonstrated in several Western populations, with this observation driven largely from European and North American cohorts (Gibson, 2009). While some researchers suggest that disease frequency has since stabilized in these areas, evidence is emerging of a dramatic rise in IBD incidence in areas from where the diagnosis was previously very rare, including throughout Asia (Thia et al., 2008).

Limited data is available on Australian IBD incidence rates. A single hospital-based study reported in 1987 suggested rates of disease in Australia were comparable to other Western populations at that time (McDermott et al., 1987). More recently, in 2003, data were published on paediatric IBD rates in Victorian hospitals, revealing a significant increase in CD incidence over a 31-year period from 0.13 to 2.0 per 100,000 (Phavichitr et al., 2003). This result represented a 15-fold increase in CD incidence during that time. However the data was derived from referral hospital records, with no confirmation of the total population at risk of disease. Subsequent to this, in 2007 Wilson et al undertook Australia’s first comprehensive, prospective, population-wide IBD incidence assessment (Wilson et al., 2010). The population examined was a geographically defined area in South-Western Victoria, around the regional city of Geelong. Using internationally accepted diagnostic criteria, the authors accurately identified 76 new cases of IBD over a 12 month period, revealing an overall incidence rate of approximately 30 per 100,000. At the time, this result was amongst the highest IBD incidence rates documented globally.

However, no local historical IBD data were available for comparison, hence the authors were not able to reflect on possible changes in local rate longitudinally. An accurate knowledge of loco-
regional fluctuations in incidence is valuable, allowing a more accurate appreciation of the predicted local disease burden. This has important implications on health resource allocation and planning. Longitudinal epidemiological observations may also reveal novel aetiological associations.

It is in this context that the current incident case identification project was designed. Specifically, we planned to examine and then compare the incidence rates and disease patterns of newly diagnosed IBD in Barwon, four years from the index study of this population.

### 4.2 HYPOTHESIS

There are two principal hypotheses for this section of the research;

1) The IBD incidence rate remains high in the Barwon region.
2) The phenotypes of newly diagnosed IBD cases will have remained relatively stable.

These propositions are based on the premise that our local rate trends should reflect those seen in other Western cohorts overseas, with similar demographic, genetic, lifestyle and environmental factors influencing disease occurrence rates and patterns.

### 4.3 AIMS

Firstly, we aimed to undertake a prospective, population-wide IBD incidence study, based on established epidemiological principles, in a geographically defined regional Australian setting.

Secondly, we aimed to directly compare incidence rates, clinical details and phenotypes of new cases from 2010-11 to locally derived IBD data from 2007-08.

### 4.4 METHODS

The methodology chosen for the incidence rate estimation study was based on the principles of observational epidemiology, details of which have already been presented in Chapter 3. Additional details on aspects of the methodology are presented in the subsequent sections.

#### 4.4.1 Study Population

The incidence study was undertaken around the city of Geelong in South Western Victoria. The population in 2010-2011 was estimated at 293,426 people. While extensive details of the study population have already been presented in chapter 3, table 4.1 and figures 4.1 and 4.2 provide additional details of the local population. Table 4.1 shows the Barwon population by 5 year age brackets. Figures 4.1 and 4.2 also present population size data for 5 year age grouping, comparing
the Barwon population with the standard WHO population. These figures demonstrate that the Barwon population is comparatively older than the global standard population, which would impact on the ability to compare our results with internationally derived data if the rates were not corrected to the standard population. This may also reduce the observed incidence of IBD in Barwon, as rates are often higher in younger age groups as previously described in chapter 2.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Barwon population %</th>
<th>Barwon population estimate</th>
<th>WHO standard populations %</th>
<th>WHO population estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>6.22</td>
<td>18253</td>
<td>8.86</td>
<td>25997.5</td>
</tr>
<tr>
<td>5-9</td>
<td>6.26</td>
<td>18378</td>
<td>8.69</td>
<td>25498.7</td>
</tr>
<tr>
<td>10-14</td>
<td>6.56</td>
<td>19244</td>
<td>8.60</td>
<td>25234.6</td>
</tr>
<tr>
<td>15-19</td>
<td>6.67</td>
<td>19578</td>
<td>8.47</td>
<td>24853.2</td>
</tr>
<tr>
<td>20-24</td>
<td>6.20</td>
<td>18181</td>
<td>8.22</td>
<td>24119.6</td>
</tr>
<tr>
<td>25-29</td>
<td>5.94</td>
<td>17423</td>
<td>7.93</td>
<td>23268.7</td>
</tr>
<tr>
<td>30-34</td>
<td>6.16</td>
<td>18081</td>
<td>7.61</td>
<td>22329.7</td>
</tr>
<tr>
<td>35-39</td>
<td>6.80</td>
<td>19940</td>
<td>7.15</td>
<td>20980.0</td>
</tr>
<tr>
<td>40-44</td>
<td>6.93</td>
<td>20341</td>
<td>6.59</td>
<td>19136.8</td>
</tr>
<tr>
<td>45-49</td>
<td>6.96</td>
<td>20432</td>
<td>6.04</td>
<td>17722.9</td>
</tr>
<tr>
<td>50-54</td>
<td>6.81</td>
<td>19972</td>
<td>5.37</td>
<td>15757.0</td>
</tr>
<tr>
<td>55-59</td>
<td>6.41</td>
<td>18801</td>
<td>4.55</td>
<td>13350.9</td>
</tr>
<tr>
<td>60-64</td>
<td>5.93</td>
<td>17392</td>
<td>3.72</td>
<td>10915.4</td>
</tr>
<tr>
<td>65-69</td>
<td>4.57</td>
<td>13407</td>
<td>2.96</td>
<td>8685.4</td>
</tr>
<tr>
<td>70-74</td>
<td>3.72</td>
<td>10918</td>
<td>2.21</td>
<td>6484.7</td>
</tr>
<tr>
<td>75-79</td>
<td>3.06</td>
<td>8992</td>
<td>1.52</td>
<td>4460.1</td>
</tr>
<tr>
<td>80-84</td>
<td>2.47</td>
<td>7248</td>
<td>0.91</td>
<td>2670.2</td>
</tr>
<tr>
<td>85-89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-94</td>
<td>All 85+ 2.33</td>
<td>6845</td>
<td>All 85+ 0.635</td>
<td>1863.3</td>
</tr>
<tr>
<td>95-99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>293,426</td>
<td>100.035%</td>
<td>293528.7</td>
</tr>
</tbody>
</table>

Table 4.1 2011 population estimates for Barwon with WHO age-standardised figure for comparison.
2011 Barwon Population by age groups

Figure 4.1 Population numbers in Barwon per age group.

2011 WHO age standardised population for comparison

Figure 4.2 World Health Organisation age standardised population.

4.4.2 Case Definition

Due to the wide differential diagnosis associated with IBD, strict diagnostic criteria were used to confirm new IBD cases, optimizing specificity for true IBD diagnosis, and hence improving the accuracy of final incidence rate calculations. As no single diagnostic test confirms a diagnosis of IBD, case confirmation relied on a composite of widely accepted clinical, radiological, endoscopic and
histological findings, as defined in table 4.2 below. The presence of criteria 1, 2, 3, 4 and 6 were mandatory, with criteria 5 providing optional support for a diagnosis of IBD. By adhering to these criteria, an attempt was made to make a diagnosis of IBD based on objective, rather than subjective, grounds. This also matched the criteria used by Wilson et al in the 2007-08 study in the same population, allowing valid comparisons of results. In addition, each new IBD case's clinical details were also compared to the Copenhagen diagnostic criteria outlined in Chapter 2, section 2.2.3.1. All cases included in the current study also met these internationally recognised criteria, validating further international comparisons with our data.

<table>
<thead>
<tr>
<th></th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Consistent clinical symptoms including abdominal pain, diarrhoea, rectal bleeding and/or weight loss for two or more weeks</td>
</tr>
<tr>
<td>2</td>
<td>Endoscopic findings including intestinal erythema, inflammation and/or ulceration that the treating clinician was satisfied was consistent with IBD</td>
</tr>
<tr>
<td>3</td>
<td>Histological confirmation of inflammation including evidence of chronicity with structural architectural changes, and/or the presence of non-caseating granuloma</td>
</tr>
<tr>
<td>4</td>
<td>Negative stool microscopy and culture results, a revision of concomitant medical history and medication use, and review of travel history in each case to exclude possible differential diagnoses including infection, ischaemia, radiation and medication related enteritis</td>
</tr>
<tr>
<td>5</td>
<td>Radiological evidence of small or large bowel inflammation or recognised IBD related complications (including erythema nodosum, pyoderma gangrenosum or any other extra-intestinal manifestation associated with IBD described previously)</td>
</tr>
<tr>
<td>6</td>
<td>Review of all case details 3 months after the index identification date to confirm the diagnosis remained constant over time, and that no new clinical features or investigation results were available that might suggest an alternative diagnosis</td>
</tr>
</tbody>
</table>

Table 4.2 IBD case definition.

Details of permanent residential addresses were collected, ensuring patients lived within the BSD at the time of the diagnosis of IBD. Final diagnostic confirmation and inclusion in the study was made only after a further review of all case notes by an independent, experienced IBD sub-specialised gastroenterologist independent from the initial case identification and record assessment (either Dr Sally Bell or Dr William Connell). Cases were excluded from the study if the diagnosis remained uncertain after considering all of the above criteria.

Ethics permission was sought to allow the principal investigator (PI) to review individually identified medical records for all suspected new cases. This occurred both within the Geelong hospital, and outside the public hospital setting in a range of private consulting rooms and pathology laboratories that were included as data sources for this research. This patient data access allowed the principal researcher to collate all relevant clinical information from several different sources to finalise the diagnosis of each new case, in addition to accurately documenting the complete phenotype for every included patient. After the case was confirmed and the full phenotypic details recorded, the name and address was removed from each record, with only initials and postcodes being ultimately
Name, date of birth, postcode and date of diagnosis were initially documented. The referral sources were recorded for each case, with both the primary source and secondary/overlapping sources recorded as necessary. Key clinical details including symptom types, and duration prior to diagnosis, were sought from the files. Other relevant personal history including smoking status, the use of concurrent medications at the time of diagnosis (particularly non-steroidal anti-inflammatory drugs) and family history were collected. The date and results of all relevant endoscopy, histopathology, medical imaging and haematology/biochemistry were noted. Relevant microbial results were recorded where available. The treating clinician’s overall impression of each case was also considered, particularly from patients identified by experienced gastroenterologists. Finally, disease severity and impact were assessed with regard to the number of hospital admissions related to IBD, need for surgery, clinician impression of disease severity, and medication use. This was performed both at baseline (within 2 weeks of diagnosis) and then at the three-month follow-up for final case confirmation. By considering all of these details, a decision on final IBD sub-type was reached, either confirming CD, UC or if the diagnosis remained uncertain, IBDU. The clinical phenotype was recorded using the previously described and validated Montreal classification system for both CD and UC (see tables 4.3 and 4.4 below, adapted from (Satsangi et al., 2006)). This phenotypic assessment was made at baseline and again at 3 months from first identification.

<table>
<thead>
<tr>
<th>Montreal</th>
<th>Extent</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Ulcerative proctitis</td>
<td>Involvement limited to the rectum (proximal extent of disease is distal to the rectosigmoid junction)</td>
</tr>
<tr>
<td>E2</td>
<td>Left sided UC (distal UC)</td>
<td>Involvement limited distal to the splenic flexure</td>
</tr>
<tr>
<td>E3</td>
<td>Extensive UC (pancolitis)</td>
<td>Involvement extends proximal to the splenic flexure</td>
</tr>
</tbody>
</table>

Table 4.3 Montreal classification of UC.
Table 4.4 Montreal classification of CD.

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.

+"p" is added to B1–B3 when concomitant peri-anal disease is present.

After complete case confirmation and phenotype description, de-identified details of cases were recorded as previously described, to comply with ethics requirements and maintain individual patient privacy and confidentiality.

4.4.3 Incident IBD Case Sources

This study incorporated the epidemiological technique of capture-recapture methodology. This relied on multiple, overlapping sources to capture the same data of interest, in this case, newly identified IBD cases. Capture-recapture methodology aimed to increase the acquisition rate for potential new cases, reduce the possibility of missing true IBD cases, and improving the overall sensitivity for case capture. Assuring the completeness of local case ascertainment was further aided by previous research performed by Dr Jarrad Wilson in this region. While undertaking the initial IBD
incidence estimation study in Barwon in 2007-08, Dr Wilson surveyed all General Practitioners in the region to assess referral patterns for when they were to suspect a new case of IBD. The vast majority referred adult patients to only local specialist doctors or hospitals. Additionally, these GP’s referred all new paediatric cases either to a local paediatrician, or to the Royal Children’s Hospital in Melbourne. With this information, it was assumed that almost all cases of new onset IBD from within the study area would be referred for workup locally, and should thus be identified by our methodology. A brief description of case referral sources are listed below.

The Geelong Hospital

The Geelong Hospital is a 406 bed regional hospital, and is the only public hospital servicing the Barwon region. In addition to providing acute Gastroenterology inpatient services, outpatient clinics and day-procedure endoscopy are also performed. A Gastroenterology Advanced Training registrar is based at the hospital, and was able to review ward/endoscopy lists daily to identify potential new IBD cases. Additionally, a number of surgical and paediatric registrars based at the hospital were contacted by telephone and email regularly during the study period, to assist in incident case identification. The author also presented an overview of the project at the Geelong Hospital’s weekly Grand Round meeting before the start of the project, raising awareness of IBD among local clinicians and to encourage referral of any new IBD cases identified throughout the hospital.

Whenever a potential case was identified, the full medical records of each case were reviewed by the author, to either exclude or verify the diagnosis, and to then accurately document disease distribution and date of diagnosis where possible. In addition to the clinician identified hospital cases, several other novel hospital-based sources of data were utilized.

Through the collaboration of a clinical pharmacist attached to the Gastroenterology service, the pharmacy department at Geelong Hospital was able to provide a series of three, 4-month, outpatient pharmacy database searches based on the dispensing of key IBD-related medications including all 5-ASA agents, Azathioprine, 6-Mercaptopurine, Infliximab and Adalimumab. Case records were then reviewed for each potential patient to exclude the use of these drugs for other diseases, most commonly for rheumatologic and dermatological conditions.

The Health Information Services (HIS) Department established a prospective and continuous disease-specific coding search that was based on defined, internationally standardised IBD-related diagnostic codes. These codes were derived from the International Classification of Diseases (ICD-10), produced by the World Health Organisation (WHO), and are outlined in table 4.5 below. The ICD-10 is the international standard for diagnostic classification, and has been developed for specific use in epidemiological study, health management purposes and also for clinical use. Each time any relevant K50/K51 related code was recorded, either as a primary or secondary diagnosis during the study
period, identifiable patient details were recorded in a dataset for later review and case confirmation by the author.

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K50.0</td>
<td>Crohn’s disease of small intestine</td>
</tr>
<tr>
<td>K50.1</td>
<td>Crohn’s disease of large intestine</td>
</tr>
<tr>
<td>K50.8</td>
<td>Other Crohn’s disease (both small and large intestine)</td>
</tr>
<tr>
<td>K50.9</td>
<td>Crohn’s disease unspecified site</td>
</tr>
<tr>
<td>K51.0</td>
<td>Ulcerative colitis pancolitis</td>
</tr>
<tr>
<td>K51.2</td>
<td>Ulcerative colitis proctitis</td>
</tr>
<tr>
<td>K51.3</td>
<td>Ulcerative colitis rectosigmoiditis</td>
</tr>
<tr>
<td>K51.4</td>
<td>Inflammatory pseudopolyps</td>
</tr>
<tr>
<td>K51.5</td>
<td>Left sided ulcerative colitis</td>
</tr>
<tr>
<td>K51.8</td>
<td>Other ulcerative colitis</td>
</tr>
<tr>
<td>K51.9</td>
<td>Ulcerative colitis unspecified</td>
</tr>
</tbody>
</table>

Table 4.5 ICD-10 based codes used in hospital based health information services search (adapted from NCCH eBook, July 2010 version).  

Finally, a prospectively maintained Division of Surgery intestinal resection database was searched at the end of the study period to identify all colorectal or intestinal surgeries that had been performed within the hospital during the study period. Case records and histology of resection specimens were reviewed to determine whether the procedure had been performed for an IBD related complication, and case details recorded as necessary.

**Gastroenterologists**

There were 7 local Gastroenterologists based in Geelong involved in case identification. Six of these were co-located in a single group practice, and one commenced solo practice during the course of the study. All specialists held public and private positions, reducing the chance of missed cases. Regular emails, phone contact and rooms visits were undertaken every 1-2 weeks during the study period to identify new cases and review the clinical details and progress of patients.

**Surgeons**

7 surgeons, including generalists and colorectal sub-specialists, covering both private and public practice, were also involved in case notification and provided access to records of potential new cases for clinical confirmation.
Paediatricians

Paediatric cases for this study were identified from both local and Melbourne-based paediatricians and paediatric gastroenterologists. Five Geelong-based paediatricians formed a large joint private practice, and also covered the Geelong public hospital paediatric ward, clinics and emergency department. They also supervised paediatric registrars within the public hospital, providing comprehensive loco-regional paediatric cover for case capture.

The Royal Children’s Hospital in Melbourne is the principal paediatric referral hospital for the state of Victoria. There were 6 paediatric gastroenterologists based at the RCH, maintaining a clinically-focused patient database of all active IBD cases. New cases from the Barwon region were readily identified from this record, and details of their clinical presentation and investigations could be reviewed. In addition, the principal paediatric gastroenterologists from the public unit also provided details of any new IBD case from the Barwon region referred to their private practices. They also facilitated contact with three other private paediatric gastroenterologists whose practices in Melbourne may have potentially seen new cases referred from within the study region.

National Paediatric IBD Registry

Dr David Moore, Head of Department of Gastroenterology at the Women’s and Children’s Hospital in Adelaide, South Australia, maintained a nationwide paediatric IBD database. Data was supplied by local clinicians throughout Australia, in a de-identified manner, and included details on place of residence place and date of IBD diagnosis. All cases from the Barwon region were successfully extracted from this national dataset, and clinical details verified as necessary from the primary clinician involved in their care.

Pathology database searches

Due to the fact that histological confirmation was required as part of our diagnostic criteria for a diagnosis of IBD, it was important to review all pathology originating from the study area over the 12-month research period. There were three pathology providers identified within the Barwon region; Healthscope, Dorevitch and St John of God (SJOG) pathology. Of these three, SJOG supplied services to the local public and private hospitals. The other two providers processed specimens from private endoscopy centres from within the study area. Retrospective searches were undertaken by pathologists from Healthscope and Dorevitch both during, and at the end of, the study period. This was based on searching pathology reports for specific codes related to IBD. These codes were derived from the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED), a comprehensive clinical terminology system that is accepted among pathology providers as an international standard for pathological diagnoses and is accepted as being reliable in its accuracy. At SJOG pathology, in addition to SNOMED searches, a dedicated histopathologist (Dr Tiffany Symes) collaborated with the author and was able to prospectively review all reports generated by the
coding search, in addition to independently reviewing and verifying results from pathology specimens as required.

**Private endoscopy centre records**

In addition to endoscopy being performed in Geelong at the public and private hospital, other regional endoscopy services were reviewed to capture cases that may have undergone their index endoscopic examination outside of the study area. Two centres were identified, Hobson’s Bay Endoscopy and Westpoint Endoscopy, both located in the city of Werribee, 42km North-East of Geelong and just outside of the Barwon boundary. Both centres maintained electronic records (Endoscribe and Bluechip Version 2.6) of all procedures performed, allowing the extraction of reports based on the endoscopist’s final diagnosis or conclusions. By cross-referencing reports generated within the study period with patient address, potential cases from within Barwon could be successfully identified. Pathology from each case was then reviewed, and either the requesting specialist or referring GP was contacted for the required clinical data and follow-up arrangements for each potential case.

**General Practitioner involvement**

Finally, 281 GP’s were found to service the study area. GP’s were regularly contacted via emails, and articles relating to the project were published in the monthly regional GP Association newsletter. In addition, the author chaired an educational session for interested GP’s to raise awareness of IBD, and to promote the referral of new cases.

**4.4.4 Ethics Approval**

The study was conducted in accordance with the Helsinki Declaration. Ethics approval for this study was granted by the Barwon Health Human Ethics Research Committee, approval number 10/50. The ethics committee deemed that individual patient consent was not required for the incidence study, on the provisos that no direct patient contact by the researchers was made, and that privacy was protected by de-identifying final stored case details.

**4.4.5 Data Recording, Storage, Analysis and Statistical Methods**

All clinical data was initially recorded manually. After final diagnostic confirmation, de-identified details on each case were then recorded electronically in an Excel spreadsheet. This dataset was maintained on a secure, password-protected computer located in the Department of Gastroenterology at St Vincent’s Hospital, Melbourne.
Crude total incidence rates were calculated for all IBD cases, with sub-type breakdowns for CD, UC and IBDU also performed. Incidence rates were calculated by using the number of new cases as the numerator, and the population at risk as the denominator. Rates were then expressed per 100,000 population. Age-standardised incidence rates were calculated using the direct method, and based on the World Health Organisation (WHO) standard population characteristics outlined previously (http://meteor.aihw.gov.au/content/index.phtml/itemId/327276). Rates were presented with 95% confidence intervals (CI) based on an assumed Poisson distribution. A direct comparison of current and historical incidence rates was made using MedCalc (MedCalc software Version 12.4; Mariakerke, Belgium). Age and duration of disease was described using frequencies, ranges and median values. Finally, comparisons between groups relating to phenotypes and clinical variables were made using Chi-square tests or Fishers exact test where appropriate. A result of p < 0.05 was considered statistically significant.

### 4.5 RESULTS

#### 4.5.1 Overview

71 new cases of IBD were confirmed during the 12 month study period. The calculated crude incidence rate for IBD in the Barwon region during 2010/2011 was 24.2 per 100,000. Table 4.6 and figure 4.3 show total incident IBD cases, demonstrating a high proportion with CD. Crude incident rates are presented in table 4.7.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>43</td>
<td>60.6%</td>
</tr>
<tr>
<td>UC</td>
<td>22</td>
<td>31.0%</td>
</tr>
<tr>
<td>IBDU</td>
<td>6</td>
<td>8.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Table 4.6 Incident cases diagnosed 2010-2011.
Figure 4.3 New IBD cases diagnosed 2010-2011.

<table>
<thead>
<tr>
<th></th>
<th>Crude incidence rates 2010-11</th>
<th>95% confidence intervals (CI's)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD Total</td>
<td>24.2 per 100,000</td>
<td>18.9 - 30.5 per 100,000</td>
</tr>
<tr>
<td>CD</td>
<td>14.7 per 100,000</td>
<td>10.6 - 19.7 per 100,000</td>
</tr>
<tr>
<td>UC</td>
<td>7.5 per 100,000</td>
<td>4.7 – 11.4 per 100,000</td>
</tr>
<tr>
<td>IBDU</td>
<td>2.0 per 100,000</td>
<td>0.8 – 4.5 per 100,000</td>
</tr>
</tbody>
</table>

Table 4.7 Crude incidence rates 2010-2011.

The case number and subsequent incidence rates were lower than those recorded in the 2007-08 study in this population, however the difference was not statistically significant. Direct comparisons between the two sets of results are presented in figure 4.4 and table 4.8 below.
Figure 4.4 Comparison of incident IBD cases in Barwon from 2007/8 and 2010/11.

Table 4.8 Comparison of current and historical crude IBD incidence rates from same population.

<table>
<thead>
<tr>
<th>IBD type</th>
<th>2007/08 crude incidence rates (95% CI’s)</th>
<th>2010/11 crude incidence rates (95% CI’s)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD Total</td>
<td>29.3 per 100,000 (23.5 – 36.7 per 100,000)</td>
<td>24.2 per 100,000 (18.9 - 30.5 per 100,000)</td>
<td>0.49</td>
</tr>
<tr>
<td>CD</td>
<td>17.4 per 100,000 (13.0 – 23.2 per 100,000)</td>
<td>14.7 per 100,000 (10.6 - 19.7 per 100,000)</td>
<td>0.72</td>
</tr>
<tr>
<td>UC</td>
<td>11.2 per 100,000 (7.8 – 16.1 per 100,000)</td>
<td>7.5 per 100,000 (4.7 – 11.4 per 100,000)</td>
<td>0.49</td>
</tr>
<tr>
<td>IBDU</td>
<td>0.8 per 100,000 (0.2 – 2.8 per 100,000)</td>
<td>2.0 per 100,000 (0.8 – 4.5 per 100,000)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

4.5.2 Age at IBD diagnosis

The age range was 13–82 years, slightly older than the age range from the 2007 study (range 9–76 years). The median age of onset of IBD was 38 years. Table 4.9 presents further details on the distribution of age across the different phenotypes. The median age of diagnosis for CD was 3 years younger than for UC.
Table 4.9 Age characteristics of incident cases.

<table>
<thead>
<tr>
<th></th>
<th>Age range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD TOTAL</td>
<td>13-82 years</td>
<td>38 years</td>
</tr>
<tr>
<td>CD</td>
<td>14-82 years</td>
<td>36 years</td>
</tr>
<tr>
<td>UC</td>
<td>13-80 years</td>
<td>39 years</td>
</tr>
<tr>
<td>IBDU</td>
<td>15-69 years</td>
<td>38 years</td>
</tr>
</tbody>
</table>

Figure 4.5 illustrates the age distribution of all IBD in the cohort, revealing disease peaks in the 15-19, 40-44 and 50-54 year age groups. While case numbers were lower over the age of 55, a late cluster of cases was noted over the age of 65 years.

![Age distribution of new IBD cases 2010/11](image)

Figure 4.5 Age distribution of incident IBD cases in Barwon 2011/12.

Figure 4.6 illustrates age of onset for different IBD phenotypes, highlighting the trend for younger age of onset, particularly for CD patients.
Figure 4.6 Age distribution of incident IBD cases in Barwon 2011/12 broken down for IBD sub-type.

Table 4.10 presents data on age of onset of disease stratified by IBD type and patient gender.

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Med age</td>
<td>39</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Female Med age</td>
<td>38</td>
<td>32</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 4.10 Median age of disease onset by IBD type and gender.

Table 4.11 and figure 4.7 present data on the crude incidence rates across specific age groupings. The peak crude IR for IBD in our population was seen between the ages of 15-24 years, with a second late rise in rates over the age of 65 years.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Population</th>
<th>IBD Total Crude Incidence rate</th>
<th>CD Crude Incidence rate</th>
<th>UC Crude Incidence rate</th>
<th>IBDU Crude Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>55875</td>
<td>7.2/100000</td>
<td>3.6/100000</td>
<td>3.6/100000</td>
<td>0/100000</td>
</tr>
<tr>
<td>15-24</td>
<td>37759</td>
<td>39.5/100000</td>
<td>29.1/100000</td>
<td>8.0/100000</td>
<td>2.7/100000</td>
</tr>
<tr>
<td>25-54</td>
<td>116189</td>
<td>34.4/100000</td>
<td>19.8/100000</td>
<td>12.1/100000</td>
<td>2.6/100000</td>
</tr>
<tr>
<td>55-64</td>
<td>36193</td>
<td>5.5/100000</td>
<td>2.8/100000</td>
<td>0/100000</td>
<td>2.8/100000</td>
</tr>
<tr>
<td>&gt;65</td>
<td>47410</td>
<td>21.1/100000</td>
<td>12.7/100000</td>
<td>6.3/100000</td>
<td>2.1/100000</td>
</tr>
</tbody>
</table>

Table 4.11 Crude incidence rates by age group.
Figure 4.7 Overall incidence rates per age grouping.

Table 4.12, figure 4.8 and table 4.13 present data on the crude and WHO age standardised incidence rates in Barwon.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Crude incidence rate Barwon 2010/11</th>
<th>Age-standardised incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>7.2/100,000</td>
<td>6.8/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>39.7/100,000</td>
<td>39.6/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>34.4/100,000</td>
<td>34.3/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>5.5/100,000</td>
<td>5.9/100,000</td>
</tr>
<tr>
<td>65+</td>
<td>21.1/100,000</td>
<td>22.0/100,000</td>
</tr>
<tr>
<td>Total all ages</td>
<td>24.2/100,000</td>
<td>24.7/100,000</td>
</tr>
</tbody>
</table>

Table 4.12 Crude and WHO age-standardised incidence rates.
Figure 4.8 WHO age-standardised incidence rates per age group.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>WHO age-standardised Incidence rate for CD</th>
<th>WHO age-standardised incidence rate for UC</th>
<th>IBDU WHO age-standardised incidence rate for IBDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>3.4/100,000</td>
<td>3.4/100,000</td>
<td>0/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>29.0/100,000</td>
<td>8.0/100,000</td>
<td>2.6/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>19.8/100,000</td>
<td>11.8/100,000</td>
<td>2.8/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>2.9/100,000</td>
<td>0/100,000</td>
<td>2.9/100,000</td>
</tr>
<tr>
<td>&gt;65</td>
<td>13.6/100,000</td>
<td>5.6/100,000</td>
<td>2.7/100,000</td>
</tr>
<tr>
<td>Total</td>
<td>15.1/100,000</td>
<td>7.5/100,000</td>
<td>2.0/100,000</td>
</tr>
</tbody>
</table>

Table 4.13 WHO age-standardised incidence rates for IBD subtypes in Barwon 2010-2011.

### 4.5.3 Gender

In this cohort of new IBD cases the overall gender distribution was relatively equal, with a total of 35 men and 36 women. Table 4.14 presents the gender-specific phenotype details, in addition to the calculated gender ratios for new onset IBD. There were more women than men diagnosed with UC, while IBDU was twice as common in men.

<table>
<thead>
<tr>
<th></th>
<th>Male (n)</th>
<th>Male (% total)</th>
<th>Female (n)</th>
<th>Female( % total)</th>
<th>Ratio (male:female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD Total</td>
<td>35</td>
<td>49.3%</td>
<td>36</td>
<td>50.3%</td>
<td>1 : 1.0</td>
</tr>
<tr>
<td>CD</td>
<td>21</td>
<td>48.8%</td>
<td>22</td>
<td>51.2%</td>
<td>1 : 1.1</td>
</tr>
<tr>
<td>UC</td>
<td>10</td>
<td>45.5%</td>
<td>12</td>
<td>54.5%</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>IBDU</td>
<td>4</td>
<td>66.7%</td>
<td>2</td>
<td>33.3%</td>
<td>2 : 1.0</td>
</tr>
</tbody>
</table>

Table 4.14 Gender distribution of new IBD cases.
4.5.4 Clinical details

Symptom duration

Reliable data on symptom duration was available on 54 patients (76% of the total incident cohort). The median duration of symptoms prior to diagnosis was 25.1 weeks, or 5.8 months. The time to diagnosis of CD was significantly longer than that for either UC or IBDU (31.6 versus 12.9 weeks \( p = 0.008 \)), as illustrated in figure 4.9.

![Median duration of symptoms](image)

Figure 4.9 Symptom duration.

Symptom types

A wide range of symptoms were recorded by referring clinicians. The most frequent symptoms in this incident cohort were diarrhoea (89%), abdominal pain (65%), and the passage of per rectum (PR) blood or mucous (62% and 34% respectively). Table 4.15 presents the frequency of the most common presenting symptoms among all IBD cases, with comparative profiles for CD and UC. Statistical comparisons between CD and UC were performed, with individual \( p \) values presented. CD patients were statistically more likely to present with abdominal pain, while those with UC had a higher frequency of PR bleeding and mucous at diagnosis. A number of less frequent symptoms were also described, the details, frequency and comparisons of which are presented in table 4.16, the frequency of which did not differ between the CD and UC cases in this cohort.
### Table 4.15 Common presenting symptoms at time of diagnosis.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All IBD cases</th>
<th>CD cases</th>
<th>UC cases</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>63 (89%)</td>
<td>38 (88%)</td>
<td>19 (86%)</td>
<td>0.552</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>46 (65%)</td>
<td>36 (84%)</td>
<td>7 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR bleeding</td>
<td>44 (62%)</td>
<td>14 (44%)</td>
<td>20 (91%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR mucous</td>
<td>24 (34%)</td>
<td>8 (19%)</td>
<td>11 (50%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (13%)</td>
<td>6 (14%)</td>
<td>3 (14%)</td>
<td>0.644</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (13%)</td>
<td>8 (19%)</td>
<td>1 (5%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18 (25%)</td>
<td>12 (28%)</td>
<td>4 (18%)</td>
<td>0.294</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (16%)</td>
<td>4 (9%)</td>
<td>0</td>
<td>0.182</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (7%)</td>
<td>4 (9%)</td>
<td>1 (5%)</td>
<td>0.445</td>
</tr>
</tbody>
</table>

### Table 4.16 Less frequent symptoms and signs at the time of IBD diagnosis.

<table>
<thead>
<tr>
<th>Symptom clinical finding</th>
<th>All IBD cases</th>
<th>CD cases</th>
<th>UC cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-anal pain</td>
<td>7 (10%)</td>
<td>7 (16%)</td>
<td>0</td>
<td>0.46</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>14 (20%)</td>
<td>10 (23%)</td>
<td>4 (18%)</td>
<td>0.448</td>
</tr>
<tr>
<td>Anaemia</td>
<td>9 (13%)</td>
<td>8 (19%)</td>
<td>1 (5%)</td>
<td>0.177</td>
</tr>
<tr>
<td>Lethargy/Fatigue</td>
<td>7 (10%)</td>
<td>7 (16%)</td>
<td>0</td>
<td>0.46</td>
</tr>
<tr>
<td>Incontinence</td>
<td>2 (3%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0.434</td>
</tr>
<tr>
<td>Faecal urgency</td>
<td>12 (17%)</td>
<td>6 (14%)</td>
<td>5 (23%)</td>
<td>0.288</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>5 (7%)</td>
<td>2 (5%)</td>
<td>2 (9%)</td>
<td>0.417</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.662</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.662</td>
</tr>
<tr>
<td>Melaena</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.662</td>
</tr>
<tr>
<td>Bloating</td>
<td>4 (6%)</td>
<td>4 (9%)</td>
<td>0</td>
<td>0.182</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.662</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.622</td>
</tr>
<tr>
<td>Pneumaturia</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.622</td>
</tr>
</tbody>
</table>
**Family History**

Data regarding family history was available on 65 patients (92% of total cohort). A family history of IBD was present in 12 cases, 17% of the total IBD cohort. CD cases were more likely to have a family history of IBD in this cohort (9 cases) than UC (1 case), with 2 cases diagnosed with IBDU having a family history of IBD. However, the small numbers precluded any statistically significant difference.

One sibling pair was diagnosed with IBD during the study period. Comparative details are presented in Table 4.17. Both had moderate/severe disease clinically, required hospital admission at the time of diagnosis, and had negative results on extensive microbial samples excluding a common infective cause for their symptoms.

<table>
<thead>
<tr>
<th>Case initials</th>
<th>CK</th>
<th>TK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Phenotype</td>
<td>IBDU - Pancolitis</td>
<td>CD – A2L3pB1*</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>9 months</td>
<td>5 months</td>
</tr>
<tr>
<td>Date of diagnosis</td>
<td>August 2010</td>
<td>September 2010</td>
</tr>
</tbody>
</table>

Table 4.17 Sibling pair diagnosed with IBD during study period.


**Smoking**

Smoking details were only available on 35 patients, representing 49% of the cohort. Four patients were recorded as current smokers, two with CD, and one each with UC and IBDU. There were 9 ex-smokers in this cohort. Being an ex-smoker was associated with a diagnosis of UC rather than CD, although this failed to reach statistical significance (p = 0.806).

**Investigation**

A wide range of investigations were used in establishing a diagnosis of IBD in this cohort. Colonoscopy was the primary mode of diagnosis in all cases. Table 4.18 outlines these investigations and their frequency of use.
<table>
<thead>
<tr>
<th>Modality</th>
<th>n (total 71 patients)</th>
<th>Percentage of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>71</td>
<td>100%</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>20</td>
<td>28%</td>
</tr>
<tr>
<td>Capsule endoscopy</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>CT scan</td>
<td>18</td>
<td>25%</td>
</tr>
<tr>
<td>Small Bowel MRI</td>
<td>8</td>
<td>11%</td>
</tr>
<tr>
<td>Small Bowel series</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>Small Bowel U/S</td>
<td>2</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 4.18 Investigations used to establish IBD diagnosis.

All cases underwent colonoscopy on at least one occasion. The next most frequently used investigations were gastroscopy and CT scanning. MRI was utilized more frequently than capsule endoscopy for the investigation of the small bowel.

**Granuloma on histology**

Histology was obtained for all new cases. In those with CD, non-caseating granuloma were identified in 17 cases, representing 40% of the total CD cohort.

**4.5.5 Phenotype breakdown**

Results of disease phenotype are presented below, using the Montreal criteria described previously.

**Phenotype in CD**

**CD BEHAVIOUR AT ONSET**

Inflammatory disease (B1) was identified in 88.4% of CD cases at diagnosis. The frequency of stricturing (B2) or penetrating (B3) disease at diagnosis was 9.3% and 2.3% respectively. Figure 4.10 illustrates disease behaviour at onset in new CD cases.
**CD Behaviour at Diagnosis Based on Montreal Classification.**

Figure 4.10

**CD LOCATION AT ONSET**

Ileocolonic disease was most frequently observed, occurring in 44% of the CD patients. Three patients (7% of all CD cases) were classified as having upper GI involvement (L4), with all of these cases also having inflammatory ileo-colonic disease (L3, B1). L4 disease was also more common at a younger age, with two cases in the A1 (<17 years) range, and one A2 (17-40 years). See figure 4.11 for further disease location details.

**Anatomical Involvement at Diagnosis of CD**

Figure 4.11
Six CD cases had perianal disease at the time of diagnosis, representing a frequency of 14% for this cohort. Table 4.19 presents the clinical details of this subgroup with perianal disease, with most patients having associated inflammatory ileocolonic disease.

<table>
<thead>
<tr>
<th>Associated behaviour</th>
<th>n</th>
<th>Percent of total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 (age &lt;17)</td>
<td>1</td>
<td>17%</td>
</tr>
<tr>
<td>A2 (age 17-40)</td>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>A3 (age &gt;40)</td>
<td>2</td>
<td>33%</td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>1</td>
<td>17%</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>1</td>
<td>17%</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>B1 (inflammatory)</td>
<td>5</td>
<td>83%</td>
</tr>
<tr>
<td>B2 (stricturing)</td>
<td>1</td>
<td>17%</td>
</tr>
<tr>
<td>B3 (penetrating)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.19 Clinical details of CD cases with perianal disease (n = 6).

**CD AGE AT ONSET**

The highest frequency of CD was in the 17-40 year age group (A2) as represented in figure 4.12.

![Montreal Criteria Age Groups at Diagnosis of CD](image)

Figure 4.12
CD PHENOTYPES BY AGE GROUP

All CD cases diagnosed at less than 17 years of age displayed inflammatory ileocolonic phenotypes, whereas those diagnosed over the age of 40 had a higher frequency of isolated ileal involvement. Further comparisons of behaviour and location for each age group are represented in figure 4.13.

A1 (AGE 0 – 16 YEARS)

A2 (AGE 17 – 40 YEARS)

Figure 4.13 Breakdown of incident case phenotypes by age groups (continued over page).
Figure 4.13 Breakdown of incident case phenotypes by age groups (continued from previous page).

Phenotype in UC
Of the 22 cases in the UC cohort, 7 (32%) presented with limited rectal disease, 6 (27%) with distal disease, and 9 (41%) with pancolonic involvement. Figure 4.14 illustrates both the total and gender specific UC phenotype distribution at diagnosis.

Figure 4.14

Data on the median age of onset for different UC phenotypes are presented in figure 4.15, illustrating in this cohort that more extensive disease (pancolitis) was significantly more frequent at presentation at a younger age (E1 + E2 median of age 46 years compared with E3 median age of 27 years, p = 0.024).


**Figure 4.15**

4.5.6 Data Sources

Clinicians within Geelong hospital, pathology record searches, and private gastroenterologist notifications were the most frequent sources of new cases. Approximately 60% of cases were identified from multiple sources, revealing a considerable overlap in case identification. Further details on sources of IBD case notification, and on the cross-capturing of cases, are presented in tables 4.20 and 4.21 respectively.

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>% of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geelong Hospital Clinicians</td>
<td>27</td>
<td>38%</td>
</tr>
<tr>
<td>SJOG Pathology</td>
<td>28</td>
<td>39%</td>
</tr>
<tr>
<td>Gastroenterology Rooms</td>
<td>23</td>
<td>33%</td>
</tr>
<tr>
<td>ICD-10 Coding</td>
<td>23</td>
<td>33%</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>Hobson’s Bay Endoscopy</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Westpoint Endoscopy</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>Royal Children’s Hospital</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>National Paediatric Database</td>
<td>3</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table 4.20 Incident IBD case sources, with total numbers (n) and frequency(%) presented (note that total % is greater than 100% due to the multiple cases sources used during this study).
Importantly, 17 new IBD cases were notified from sources other than the Geelong hospital clinicians, pathology database searches, and the Geelong gastroenterologists (representing 24% of all new cases). This emphasises the importance of collecting data from additional sources to maximise ascertainment rates. Details of where additional cases were referred from is presented in table 4.22.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>% of total cohort (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geelong hospital coding</td>
<td>6</td>
</tr>
<tr>
<td>Geelong hospital pharmacy</td>
<td>5</td>
</tr>
<tr>
<td>RCH</td>
<td>4</td>
</tr>
<tr>
<td>SA Database</td>
<td>3</td>
</tr>
<tr>
<td>Hobson’s Bay endoscopy</td>
<td>5</td>
</tr>
<tr>
<td>West Point endoscopy</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4.22 Additional case yield from data sources outside of the main referral base of Geelong gastroenterologists, Geelong hospital clinical staff and pathology database searches.

### 4.5.7 Paediatric Cohort Analysis

For reasons described in the discussion section of this chapter, an age of 19 or less was used to define paediatric onset IBD. 13 patients were diagnosed in this age group, representing 18% of the total IBD cohort. The median age of onset in the paediatric cohort was 16 years. There was a slight male predominance (54% male versus 46% female).

CD was the predominant subtype of IBD diagnosed (70% of cases). Irrespective of the final subtype classification, there was a strong association with colonic involvement in this cohort. Further details, including case numbers, sub-types and disease location, are presented in table 4.23 and figure 4.16.
Table 4.23 Paediatric incident case details.

<table>
<thead>
<tr>
<th>Population</th>
<th>Total IBD cases</th>
<th>CD cases</th>
<th>UC cases</th>
<th>IBDU cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>75453</td>
<td>13</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Paediatric Cohort IBD Sub-types

- CD n=9
- UC n=3
- IBDU n=1

Paediatric Cohort IBD Location

- Colonic n=12
- Extra-colonic n=1

Figure 4.16

A detailed comparison of phenotypes and disease distribution between the paediatric and the adult cohorts are presented in Table 4.24.

<table>
<thead>
<tr>
<th>Disease localisation for paediatric and adult patients (excluding IBDU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Localisation CD</td>
</tr>
<tr>
<td>L1 (ileal)</td>
</tr>
<tr>
<td>L2 (colonic)</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
</tr>
<tr>
<td>L4 (upper GI alone)</td>
</tr>
<tr>
<td>L1+L4 (upper GI + ileal)</td>
</tr>
<tr>
<td>L2+L4 (upper GI + colonic)</td>
</tr>
<tr>
<td>L3+L4 (upper GI + ileocolonic)</td>
</tr>
<tr>
<td>p (perianal)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Localisation UC</th>
<th>Paediatric UC n = 3</th>
<th>Adult UC n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>0</td>
<td>7 (36%)</td>
</tr>
<tr>
<td>E2</td>
<td>0</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>E3</td>
<td>3 (100%)</td>
<td>6 (32%)</td>
</tr>
</tbody>
</table>

Table 4.24 Comparison of paediatric and adult incident cases from 2010/11 Barwon cohort.
The total crude IBD incidence rate for the paediatric cohort was 17.2/100,000, with further rate details presented in table 4.25.

<table>
<thead>
<tr>
<th>Population</th>
<th>Total IBD IR</th>
<th>CD IR</th>
<th>UC IR</th>
<th>IBDU IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>75453</td>
<td>17.2/100000</td>
<td>11.9/100000</td>
<td>4.0/100000</td>
</tr>
</tbody>
</table>

**Table 4.25** Crude paediatric IBD incidence rates in Barwon 2010/11.

A family history of IBD was observed in 4 cases (31% of paediatric cohort). All paediatric cases had a documented history of diarrhoea and abdominal pain. More paediatric onset IBD patients were anaemic at the time of diagnosis compared with their adult counterparts. Further details regarding symptoms at the time of diagnosis are outlined in tables 4.26 and 4.27.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>PR bleeding</td>
<td>9 (70%)</td>
</tr>
<tr>
<td>PR mucous</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4 (30%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

**Table 4.26** Common presenting symptoms at time of diagnosis in paediatric patients.

<table>
<thead>
<tr>
<th>Anaemia at diagnosis</th>
<th>Paediatric</th>
<th>Adult</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 cases (23% of cohort)</td>
<td>6 cases (10% of cohort)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Table 4.27** Comparison of anaemia rates between paediatric and adult cases of new onset IBD.

Colonoscopy was the principal diagnostic tool used in the paediatric IBD cohort (100% of cases). Table 4.28 outlines the other investigations utilized in making the diagnosis of IBD in the paediatric cohort.
<table>
<thead>
<tr>
<th>Modality</th>
<th>n = 13</th>
<th>Percentage of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>13</td>
<td>100%</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>6</td>
<td>46%</td>
</tr>
<tr>
<td>Capsule endoscopy</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>CT scan</td>
<td>2</td>
<td>15%</td>
</tr>
<tr>
<td>Small Bowel MRI</td>
<td>2</td>
<td>15%</td>
</tr>
<tr>
<td>Small Bowel series</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Small Bowel U/S</td>
<td>1</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 4.28 Investigation modalities used during the diagnostic work-up of new paediatric IBD patients.
4.6 DISCUSSION

This study has demonstrated stable high IBD incidence rates in a large regional Australian population. It is important because it used similar IBD case definitions and case capture methodology as the local historical incidence study from this region, allowing accurate longitudinal incidence and phenotype monitoring. The results support the reliability of the methodology used.

The absolute incidence rates of total IBD, CD and UC from the current study were less than those found in the 2007-08 study. Conversely, the rate of IBDU increased from 0.8 to 2.0 per 100,000. However, further analysis revealed that these differences did not reach statistical significance, with a wide overlap in the 95% confidence intervals between the two cohorts. This suggests that the IBD incidence rate has remained stable in this population over the last 3 years.

Data from the current cohort shows that IBD in this region has bimodal peaks in incidence, affecting both young people (predominantly CD) and also those over the age of 65. In addition, a significant number have a severe disease phenotype that is likely to require either surgery or intensive medical therapy in the future.

One of the strengths of this study is the clinically-focused, population-based prospective nature of the research, and is comparable to that used in other high quality Australian, New Zealand, North American and European research. This approach eliminates many of the potential biases that were inherent to previous studies that may have been either retrospective, or have relied purely on hospital-derived or insurance generated coding data that lacked clinical case confirmation. The strength of the methodology used for this current research further allows valid and reliable comparisons with contemporary international population-based epidemiological IBD studies.

When compared to previous international data, the rate of new onset IBD in this population remains relatively high, with crude IBD incidence rates of 24.2 per 100,000. Table 4.29 provides age-standardised comparative rates from other recent similarly designed large-scale epidemiology studies.
A number of possible explanations exist for the continued observation of high IBD rates in this local population.

Firstly, the population genetic pool should be considered. Many studies have reported on the link between IBD and race, ethnicity and genetic factors (Basu et al., 2005, Van Limbergen et al., 2007, Shih and Targan, 2009). Further analysis of the residents living in Barwon show most are descended from European heritage, sharing similar genetic attributes to other western populations with similar high rates of IBD.

Secondly, the possibility of a strong local environmental trigger for IBD in this region remains. A number of such triggers have been previously suggested, with particular interest in the role of microbes on mucosal inflammation (Mayer, 2010). The observation of one sibling pair with newly diagnosed IBD within a short time frame suggests a possible shared exposure in these two cases, while also possibly sharing a common genetic risk for IBD.

Thirdly, ‘lifestyle’ of a population has been recognised as having a possible role in IBD aetiology (Mayer, 2010). The lifestyle of the population living in Barwon is typically ‘Western’, with the majority of people living in an urban environment and consuming a typical western diet high in refined sugars and fats and low in fibre and unprocessed foods, previously linked to the possible onset of IBD (Chapman-Kiddell et al., 2010). Urbanisation is associated with improved hygiene and sanitation, reducing the exposure of the population to a range of potential pathogens. This has an impact on immune development, particularly during childhood, and forms the basis of the ‘Hygiene Hypothesis’ of disease pathogenesis (Strachan, 1989). It is proposed that the subsequent immune

<table>
<thead>
<tr>
<th>Location</th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barwon, Victoria, Australia 2011</td>
<td>24.7</td>
<td>15.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Barwon, Victoria, Australia 2008 (Wilson et al., 2010)</td>
<td>29.6</td>
<td>17.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Denmark 2005 (Jacobsen et al., 2006)</td>
<td>29.2</td>
<td>16.3</td>
<td>12.9</td>
</tr>
<tr>
<td>New Zealand 2004 (Gearry et al., 2006)</td>
<td>25.2</td>
<td>16.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Canada 2000 (Bernstein et al., 2006)</td>
<td>23.1</td>
<td>8.6</td>
<td>13.4</td>
</tr>
<tr>
<td>United Kingdom 2000 (Rubin et al., 2000)</td>
<td>22.2</td>
<td>8.3</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Table 4.29 Comparison of recent global WHO age-standardised incident rates (expressed as cases per 100,000).
regulation changes seen with improved hygiene predispose these populations to a range of auto-immune type illnesses, including IBD (Koloski et al., 2008).

While significant increases in IBD incidence in developing regions of the world have recently been demonstrated, data from developed or Westernised nations suggest that loco-regional incidence rates in first-world countries may have stabilised (Bernstein et al., 2006, Engal and Neurath, 2010). Our current results provide further support of a possible plateau in incidence rates in developed countries. The reason for this remains unclear.

The ratio of CD compared to UC is noteworthy. The overall predominance of CD in this cohort (61% CD and 31% UC) has been similarly observed in a number of other western cohorts including those from Canada (Bernstein and Nabalamba, 2006). Conversely, recent Danish data revealed higher rates of UC in their local population (Vind et al., 2006). In general, higher rates of UC are identified in regions where IBD is emerging, most notably in developing nations, possibly reflecting on different pathogenic pathways between the two conditions (Bernstein et al., 2010a). However, a concise explanation of these geographical differences has not yet been defined.

In our cohort, the absolute proportion of UC was less that that found in the 2008, however the proportion of IBDU was higher. While this may be a true observation reflecting a change in local disease phenotype pattern, it may also relate to limitations resulting from the relatively small cohort size and the subjective nature of deciding on the final phenotype classification. Table 4.30 further summarizes some of the clinical and demographic differences between the 2007-08 and 2010-11 cohorts, although it is important to note that none of these differences reached statistical difference.

<table>
<thead>
<tr>
<th></th>
<th>2007-08 cohort</th>
<th>2010-11 cohort</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD cases n</td>
<td>76</td>
<td>71</td>
<td>n/a</td>
</tr>
<tr>
<td>CD cases n</td>
<td>45 (59%)</td>
<td>43 (61%)</td>
<td>0.501</td>
</tr>
<tr>
<td>UC cases n</td>
<td>29 (38%)</td>
<td>22 (31%)</td>
<td>0.230</td>
</tr>
<tr>
<td>IBDU cases n</td>
<td>2 (3%)</td>
<td>6 (8%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>43 (57%)</td>
<td>36 (51%)</td>
<td>0.236</td>
</tr>
<tr>
<td>CD median age</td>
<td>34 years</td>
<td>36 years</td>
<td>0.340</td>
</tr>
<tr>
<td>UC median age</td>
<td>43 years</td>
<td>39 years</td>
<td>0.903</td>
</tr>
<tr>
<td>Pts &lt; 21 years n (%)</td>
<td>14 (18%)</td>
<td>15 (21%)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Table 4.30 Barwon region incident cohort demographic comparisons.
The design of the current study allowed detailed and accurate phenotypic and clinical data to be captured. This provided the opportunity for reliable and novel observations from within this cohort, and the subsequent comparison of details with other similarly derived IBD incident cohorts.

The peak crude incidence rate for CD in our population was seen in the 15-24 year age group, with a rate of 29.1/100,000, while the peak rate for UC was observed in the 25-54 year age group, with a rate of 12.0/100,000. There is variability in the literature with regard to age and gender influences on IBD onset. For instance, when examining the results from the New Zealand Canterbury epidemiology study from 2004, there was a 5 year difference in age at diagnosis for women with CD compared to UC (30 versus 35 years) (Gearry et al., 2006). A recent Danish population-based cohort revealed a median age of IBD onset of 36 years (Vind et al., 2006). In this study the median age of onset for CD was 31 years, and for UC 38 years. Wilson et al demonstrated a 9 year difference for median age of onset for CD compared with UC in the local Barwon region (34 versus 43 years), however did not report on gender specific rates (Wilson et al., 2010). By comparison, in the current 2010-2011 cohort, the median age of onset for CD was 36 years and for UC 39 years, with the overall median onset of IBD of 38 years. This is likely to reflect the relatively small sample size of the cohort, rather than a true change in disease behaviour and onset in the local population.

A bimodal pattern of IBD incidence rates has previously been described (Farrokhyar et al., 2001). Although the small cohort size limited statistical analysis, a trend toward a late peak in IBD incidence was also demonstrated in the current cohort, becoming evident over the age of 65 years for both CD and UC.

A number of possible explanations for age-specific observations exist. Detailed review of the CD cohort from the current study reveals a cluster of cases diagnosed over the age of 65, having a significant impact on median age results due to the relatively small cohort being studied. Furthermore, reviewing the gender-specific results for IBD phenotypes provides further explanations for the observed differences. The median age of CD diagnosis in men was 41 years, while the median age for UC in men in this cohort was only 38. Conversely, for women the median age of onset of CD was 32 years, while for UC it was 44 years, a result more in keeping with previous publications. The current incident cohort had a very high number of men diagnosed at an advanced age with CD, with comparatively few older diagnoses of UC. In fact, of the 21 men diagnosed with CD, over half (11 out of 21, or 52%) were diagnosed over the age of 40. Similarly, no men were diagnosed with UC over the age of 46 years, further influencing the calculated age differences in this small cohort.

When considering the age standardised rates for this population, a relatively high incidence was observed in the older age group. Significantly, an older age at IBD onset has recently been linked to prognosis, with worse clinical outcomes, higher hospitalisation rates and increased mortality rates
observed (Ananthakrishnan et al., 2009). The local result may therefore have important implications with regard to potential health care resource utilisation and costs in this population.

The current cohort revealed an even gender distribution for IBD, with 50.7% cases female and 49.3% male. No significant differences were observed when considering the gender distribution of IBD sub-phenotypes. Although IBD was previously considered more common in women, recent publications regarding the influence of gender on IBD frequency have shown a relative equalisation of rates between genders (Vind et al., 2006).

Reliable details regarding disease distribution were available for the current cohort. With regards to UC, the frequency of rectal disease (E1) was 32%, left-sided or distal disease (E2) 27%, and extensive or pancolonic disease (E3) 41%. For CD, ileal location (L1) occurred in 30%, colonic disease (L2) 26% and ileo-colonic disease (L3) 44%. The majority had uncomplicated, inflammatory disease (B1 on Montreal classification). Fourteen percent of the cohort had evidence of peri-anal disease at diagnosis, and 7% had upper GI involvement in combination with disease elsewhere in the GI tract. No cases of isolated upper GI disease were diagnosed in this cohort.

Direct comparison of the phenotypic details from the current study to previously published results is difficult due to methodological heterogeneity and comparative population inconsistencies. For example, Lakatos et al recently published extensive clinical details on incident IBD cases from 2002 until 2006 in Western Hungary, with some differences in disease patterns different to those observed in the current Barwon cohort (Lakatos et al., 2011). They observed UC phenotypes of proctitis 27%, distal colitis 51% and extensive or pancolitis in 22%. For CD, isolated ileal involvement occurred in 20%, with colonic 36% and ileocolonic location in 44%. Their rate of perianal disease was 11%. With regards to CD behaviour, they found a significantly higher proportion of cases had non-B1 disease, indicating a more complicated phenotype. However these differences are likely to relate to the fact that their results were mainly hospital-based, and are prone to the influence of case selection bias.

A recent publication on consecutive population-based CD incident cases from Northern France demonstrated a number of similarities with the current Barwon cohort (Chouraki et al., 2011). Phenotypic comparison details are presented in table 4.31.
Disease localisation comparison for CD between Barwon cohort and the Chouraki cohort from Northern France*

<table>
<thead>
<tr>
<th>CD Localisation</th>
<th>2007 French CD cohort</th>
<th>2011 Barwon CD cohort</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 631 (% of cohort)</td>
<td>n = 43 (% of cohort)</td>
<td>n/a</td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>84 (16%)</td>
<td>13 (30%)</td>
<td>.005</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>29 (5%)</td>
<td>11 (26%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>L3 (ileo-colonic)</td>
<td>244 (45%)</td>
<td>19 (44%)</td>
<td>.287</td>
</tr>
<tr>
<td>L1+L4 (ileo + upper GI)</td>
<td>41 (8%)</td>
<td>0</td>
<td>.061</td>
</tr>
<tr>
<td>L2+L4 (colonic + upper GI)</td>
<td>18 (3%)</td>
<td>0</td>
<td>.300</td>
</tr>
<tr>
<td>L3+L4 (ileo-colonic + upper GI)</td>
<td>126 (23.2%)</td>
<td>3 (7%)</td>
<td>.021</td>
</tr>
<tr>
<td>p (perianal)</td>
<td>91 (12%)</td>
<td>6 (14%)</td>
<td>.574</td>
</tr>
</tbody>
</table>

Table 4.31 Disease comparisons between French and Victorian cohorts.
*(Chouraki et al., 2011)*

The two cohorts showed similarly high proportions of L3 disease. The frequency of perianal involvement was also closely matched. However, more cases in the French study exhibited upper GI involvement (L4 phenotype). Rather than a true difference, this may reflect a case inclusion bias. The French study only included new CD cases which had undergone ‘complete bowel examination’. This was loosely defined by the authors as obtaining images of both the small and large bowel, however specific details as to the extent of small bowel visualisation remain unclear. Therefore, more extensive small bowel investigation in the French cohort may have biased the results toward detecting more L4 disease, whereas the Barwon cohort phenotypic details were presented on all confirmed cases irrespective of whether full small intestinal imaging was obtained by the referring clinician. The Barwon cohort did have significantly higher rates of isolated ileal or purely colonic disease. The reason for this is unclear, however may reflect true differences in disease phenotype or relate to the relatively smaller cohort size from Barwon.

A more reliable comparison with the current 2010/11 cohort is possible when reviewing results from the incident cohort derived from the same region by Wilson et al from 2007 to 2008, using similar
methodology to the current study (Wilson et al., 2010). Table 4.32 provides a comparison of phenotypes between the two cohorts.

<table>
<thead>
<tr>
<th>Disease localisation comparison for CD, UC and IBDU between the 2008* and 2011 IBD incidence studies in Barwon, Australia.</th>
<th>2007/08 cohort</th>
<th>2010/11 cohort</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD Localisation</strong></td>
<td>n = 45 (% of CD cohort)</td>
<td>n = 43 (% of CD cohort)</td>
<td></td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>22 (49%)</td>
<td>13 (30%)</td>
<td>.058</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>12 (27%)</td>
<td>11 (26%)</td>
<td>.551</td>
</tr>
<tr>
<td>L3 (ileo-colonic)</td>
<td>11 (24%)</td>
<td>19 (44%)</td>
<td>.042</td>
</tr>
<tr>
<td>L4 (isolated upper GI)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>L1+L4 (ileal + upper GI)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>L2+L4 (colonic + upper GI)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>L3+L4 (ileo-colonic + upper GI)</td>
<td>0</td>
<td>3 (7%)</td>
<td>.112</td>
</tr>
<tr>
<td>p (perianal)</td>
<td>n/a</td>
<td>6 (14%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>UC Localisation</strong></td>
<td>n = 29 (% of UC cohort)</td>
<td>n = 22 (% of UC cohort)</td>
<td></td>
</tr>
<tr>
<td>E1 (proctitis)</td>
<td>10 (35%)</td>
<td>7 (32%)</td>
<td>.542</td>
</tr>
<tr>
<td>E2 (distal colitis)</td>
<td>14 (48%)</td>
<td>6 (27%)</td>
<td>.109</td>
</tr>
<tr>
<td>E3 (panceolitis)</td>
<td>5 (17%)</td>
<td>9 (41%)</td>
<td>.060</td>
</tr>
<tr>
<td><strong>IBDU</strong></td>
<td>n = 2 (3% of total cohort)</td>
<td>n = 6 (8% of total cohort)</td>
<td>.242</td>
</tr>
</tbody>
</table>

Table 4.32 Comparison between the 2007/08 and 2010/11 Barwon IBD incident case cohorts.
*(Wilson et al., 2010)

Although most of the differences failed to reach statistical significance, there was a trend toward higher rates of colonic involvement in the more recent cohort, for both CD and UC. For instance, when considering UC, the present cohort had higher rates of extensive (E3) disease (41% versus 17%, p = 0.06). For CD cases, the 2011 cohort had less isolated ileal (L1) disease (30% versus 49%. P =
0.058) and more ileo-colonic (L3) disease (44% versus 24%, p = 0.042). This change in disease location may have a significant impact on disease prognosis, as evidence has recently suggested a more complicated course with ileo-colonic disease than previously appreciated (Walfish and Sachar, 2007). While the observed changes in the local population may represent true changes in local disease distribution and pathogenesis, the variations identified may also be a consequence of the relatively small cohort sizes being compared, and the short time interval between the two studies.

The presence of granuloma on histology is considered a hallmark of CD, however they are not universally seen in all cases (Thoreson and Cullen, 2007). Estimates of the frequency of granuloma in newly diagnosed CD patients range from 40-60%, but drops to 15-36% when considering biopsy samples rather than surgical specimens (Engal and Neurath, 2010). The result from the current study, with granuloma identified in 40% of new CD cases, are similar to published figures, despite the fact that most granuloma were identified on biopsy samples rather than full surgical resection specimens in this cohort.

The median duration of symptoms in the current study were longer than those described previously in the 2008 cohort (25 versus 12 weeks, p < 0.001). This is likely to be multifactorial. In the current cohort, the maximal symptom duration was 12 years. This was in a patient presenting with infrequent, intermittent small bowel obstruction. Similarly, many other cases in the current cohort described very intermittent symptoms, further delaying their diagnosis. The current study did, however, suggest that those presenting with CD had a significantly longer duration of symptoms than those with UC (31.6 and 12.9 weeks respectively, p = 0.008). A review of symptom duration from a population-based cohort in Denmark from 2003/04 showed a similar pattern of disease duration, with median symptoms for CD and UC of 36 and 20.6 weeks respectively (Jess et al., 2007). The longer delay for diagnosis of CD was also demonstrated by Vind et al, with the median time to diagnosis of CD 8.3 months compared to 4.5 months for UC (Vind et al., 2006). While the observed difference may possibly reflect the different nature of symptoms related to colonic inflammation, the highly subjective nature of retrospective recollections regarding disease onset in these older studies makes reliable interpretation difficult.

Over the entire IBD cohort, the most common symptoms were diarrhoea, abdominal pain, and the passage of PR blood and mucous. Those with a diagnosis of CD were more likely to have abdominal pain, nausea, weight loss and fever, while UC patients had higher rates of PR bleeding, PR mucous, tenesmus and faecal urgency. The presence of perianal pain, fatigue and/or lethargy occurred exclusively in those with CD. While the frequency of iron deficiency was similar between the two groups, anaemia was seen more frequently in CD patients. These differences, however, should be interpreted with caution, as they rely on the appropriate documentation by referring clinicians, are often subjective in nature, and may have been subject to recall bias.
Some of the symptom patterns observed in this IBD cohort have been previously recognised. For instance, diarrhoea has been consistently observed to be the most common symptom related to IBD (Engal and Neurath, 2010). In addition, Kugathasan et al analysed data from a large population-based paediatric IBD cohort, confirming abdominal pain was more common in CD, while rectal bleeding was more commonly associated with UC (Kugathasan et al., 2003). They also found a stronger association between fatigue and CD, rather than with UC. Bernstein et al previously reported that a higher proportion of CD patients presented with nausea and vomiting, a finding also replicated in the current 2010-11 Barwon cohort (Bernstein et al., 2010a).

Diarrhoea and abdominal pain were the most common symptoms in children in this study, confirming results previously published by Dubinsky et al in a review of presentation symptoms in paediatric IBD populations (Dubinsky, 2008). When comparing adult to paediatric cases from the current cohort, diarrhoea was the most frequent symptom in adults, whereas abdominal pain was identified in all of the paediatric patients, regardless of IBD sub-type. This replicates a similar pattern of symptoms published by Caprilli et al in a 2006 ECCO consensus statement, and also by Sawrzenko et al in 2003 (Caprilli et al., 2006, Sawrzenko and Sancho, 2003).

A family history of IBD was documented in 17% of the current cohort. This is identical to the frequency of family history from the 2004 Canterbury study (Gearry et al., 2006). In our cohort the association with family history was strongest for CD.

Only a small proportion of newly diagnosed cases in this study smoked. This, combined with the small size of the entire cohort, make interpretation of the influence of smoking on IBD development in this population difficult. Despite this, a trend toward higher rates of UC in ex-smokers was observed. This trend has previously been reported, with the greatest risk for developing UC appearing to be within the first three years from quitting (Ali and Tamboli, 2008). This detailed level of smoking-related information was not available for the current cohort due to the observational nature of the study, with data being obtained from referring clinician’s records rather than direct patient questioning.

A range of diagnostic modalities were used in the work-up of possible IBD cases in the 2010-11 Barwon cohort. However, this was not designed to assess the diagnostic capabilities or yield of IBD investigations. Rather, it provided an opportunity to observe and report on local investigation choices in a ‘real-world’ Australian setting. All cases underwent colonoscopy, the minimum investigation required in most diagnostic guidelines (Engal and Neurath, 2010). Just under one third also underwent upper GI endoscopy. A recent publication recommended upper GI endoscopy in all potential new IBD cases to allow full staging of disease and confirmation of phenotypic assessment (Engal and Neurath, 2010). A quarter of the cohort underwent CT scanning during diagnostic work-up, a significant issue to consider in relation to the complications of radiation exposure in the long-
term inherent to IBD patients with chronic, complex diseases requiring multiple investigations over time.

The approach to investigate possible small bowel disease in this cohort was variable. This may reflect on the previous lack of clear recommendations on small bowel imaging modalities with regards to sensitivity, specificity, risk and cost (Ali and Tamboli, 2008), although a recent publication has provided some guidance to clinicians in this area (Allen et al., 2011). Dedicated small bowel MRI was used in 8 cases, in comparison to only 2 small bowel series, suggesting that the newer technique of MRI is preferred by local clinicians. Small bowel ultrasounds were performed in only two cases, reflecting on difficulties accessing operators experienced in performing and reporting on this technique. Wireless capsule endoscopy (WCE) was performed in 5 cases, highlighting the increasing role of this new technology in the diagnostic work-up of IBD. It should be noted that access to WCE in Australia is highly regulated. Funding for WCE is tightly controlled, and the assessment or work-up of possible IBD is not currently included as a recognised indication. This access issue is likely to have influenced the rate of WCE use in the current study. In addition, on a practical level, the clinical and diagnostic significance of subtle small bowel ulceration or inflammation identified during WCE remain unknown. Importantly, in this current cohort all cases with suspicious findings on capsule endoscopy fulfilled traditional IBD diagnostic criteria outlined in section 4.3.2.

Finally regarding investigations, serologic or faecal markers were not used as part of the investigation of possible IBD symptoms in the current cohort. This may once again relate to local issues regarding access and cost, however it is also likely to reflect local clinician uncertainty with how these new techniques will assist in the diagnostic work-up of IBD.

A detailed review of the paediatric IBD subgroup from the 2010-11 Barwon cohort provides some novel insights. Before comparing these results with previously published paediatric IBD cohort data, it is important to consider how paediatric IBD was defined. A wide age range has been used to previously define paediatric-onset IBD, ranging from under 14 up to 20 years of age (Benchimol et al., 2010). For example, in a large, well designed population-based French study from 2005 the authors chose an age limit of 17 (Auvin et al., 2005). In 2006, Bernstein et al published one of the largest population-based epidemiological studies in recent times, and chose to define paediatric disease in this population as an onset prior to the age of 20 (Bernstein et al., 2006). The variation in how paediatric IBD has been defined limits the comparability of many paediatric IBD epidemiological studies. A recent review suggests using the higher age cut-off to define paediatric-onset IBD is valid (Benchimol et al., 2010). After considering this recent guideline, and due to similarities in methodology between the 2006 Bernstein study and the current project, the 0-19 age range was chosen for the current study to define paediatric onset IBD.

The crude paediatric IBD incidence rate for the current cohort was 17.2 per 100,000. When considering the most recent paediatric IBD epidemiological studies, IBD incidence rates from 6 – 15
per 100,000 have been published. The results from the current Barwon cohort confirm a comparatively high IR in the local paediatric population. More extensive paediatric IBD rate comparisons are presented in table 2.10 in chapter 2.

Our updated results suggest there has been a significant rise in rates of paediatric IBD in Australia. For example, the crude incidence rate for CD of 11.9 per 100,000 for the 2010-11 cohort is higher that the crude CD rate of 2.0 per 100,000 published from the Royal Children's Hospital in Melbourne from 2003 (Phavichitr et al., 2003). However, issues relating to differences in study design may limit direct comparability between these studies as the second cohort was not population-based. Although the international evidence on time trend changes is conflicting, recent data from the population-based IBSEN cohort from South-East Norway suggest a recent significant rise in CD incidence in children in that population (Perminow et al., 2006).

When directly comparing paediatric to adult onset IBD, some important differences are noted. In the 2010-11 Barwon paediatric cohort the majority of disease activity was located in the colon, irrespective of the final IBD sub-type (CD or UC). This observation of high rates of colonic involvement has also been demonstrated in international cohorts (Benchimol et al., 2010), and is further expanded on in the following sections. The frequency of peri-anal disease, recognised as a surrogate marker of severity, was higher in the current paediatric cohort when compared to adult patients, although this difference failed to reach statistical significance (22% versus 12%, p = 0.301). Together, these findings suggest a more aggressive disease phenotype in children.

Jacobsen et al recently published comparative work reviewing clinical differences in paediatric and adult IBD at disease onset from population-based Danish cohorts (Jakobsen et al., 2011). A summary of their findings, including a direct comparison with the current 2010-11 Barwon IBD cohort, are represented below in tables 4.33a (paediatric) and 4.33b (adult). Despite the smaller sample size from the current Barwon cohort, several important observations are noted. Firstly, the observation of more extensive disease at the time of UC diagnosis in paediatric patients compared to adult patients is clear in both regions. This finding is further supported by results from a 2003 study from Wisconsin, USA, showing pancolitis in 90% of new onset UC in a large paediatric cohort (Kugathasan et al., 2003). Regarding CD, the frequency in isolated ileal disease was similar between the Danish and Australian paediatric cohorts. However, the adult Danish cohort had lower rates of ileal disease than the adult Barwon cohort (19% versus 35%, p = 0.068). Adult and paediatric patients from the Barwon cohort had statistically higher frequencies of ileocolonic disease than Danish patients. The paediatric Barwon cohort had a higher frequency of upper GI involvement (L4 on the Montreal classification system) than Barwon adults, whereas the rates of L4 disease were similar in Danish children and adults. However, the Barwon cohort was small compared with the Danish cohort, and variations in the precise definitions of disease location and use of small bowel investigations between the groups may have also influenced the observed differences.
<table>
<thead>
<tr>
<th></th>
<th>Danish Cohort (2001-06)*</th>
<th>Barwon Cohort (2010-11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paediatric</td>
<td>Paediatric</td>
<td></td>
</tr>
<tr>
<td><strong>CD Localisation</strong></td>
<td>n = 29</td>
<td>n = 9</td>
<td></td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>4 (14%)</td>
<td>1 (11.1%)</td>
<td>.662</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>9 (31%)</td>
<td>1 (11.1%)</td>
<td>.233</td>
</tr>
<tr>
<td>L3 (ileo-colonic)</td>
<td>10 (34%)</td>
<td>7 (78%)</td>
<td>.028</td>
</tr>
<tr>
<td>L4 (isolated upper GI)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>L1+L4</td>
<td>2 (7%)</td>
<td>0</td>
<td>.578</td>
</tr>
<tr>
<td>L2+L4</td>
<td>2 (7%)</td>
<td>0</td>
<td>.578</td>
</tr>
<tr>
<td>L3+L4</td>
<td>2 (7%)</td>
<td>2 (22%)</td>
<td>.233</td>
</tr>
<tr>
<td>L1+L4+L2+L3</td>
<td>n/a</td>
<td>2 (22%)</td>
<td>-</td>
</tr>
<tr>
<td>UC Localisation</td>
<td>n = 20</td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>E1 (proctitis)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>E2 (distal colitis)</td>
<td>6 (30%)</td>
<td>0</td>
<td>.384</td>
</tr>
<tr>
<td>E3 (pancolitis)</td>
<td>14 (70%)</td>
<td>3 (100%)</td>
<td>.384</td>
</tr>
</tbody>
</table>

**Table 4.33a** Comparing IBD distribution between recent Danish and Victorian IBD cohorts – Paediatric cases.

*(Jakobsen et al., 2011)*
Table 4.33b Comparing IBD distribution between recent Danish and Victorian IBD cohorts – Adult cases.

*Jakobsen et al., 2011

The ESPGHAN inflammatory bowel disease working group has previously published practice guidelines for the diagnosis of childhood IBD (2005). These authors suggest that every child suspected of having IBD should undergo colonoscopy in addition to upper GI endoscopy and extensive tissue biopsy. They also recommend contrast-assisted small bowel imaging unless a diagnosis of UC is thought to be definite. While the current Barwon paediatric cohort underwent gastroscopy more frequently than local adult IBD patients (46% versus 28%), the rate of gastroscopy still falls short of the ESPGHAN recommendations. In addition, not all cases in the current paediatric cohort underwent complete small bowel assessment during the study period.

Rates of anaemia in the paediatric sub-cohort in this study were higher than those observed in adult patients. This finding is supported by a recent study published by Goodhand et al, who demonstrated significantly higher rates of anaemia in paediatric IBD patients compared to their adult counterparts (Goodhand et al., 2011). However, the population in that trial had an established
diagnosis of IBD, making the finding of higher rates at the point of diagnosis in the current Barwon study novel.

A stronger association with a family history of IBD was observed in the current Barwon paediatric cohort, with 31% of paediatric cases having a family history of IBD, compared to 14% of adult patients, although this did not reach statistical significance due to small sample size \((p = 0.181)\). By comparison, 11% of new paediatric IBD cases had a positive family history in the previously described population-based paediatric cohort from Wisconsin in the USA (Kugathasan et al., 2003). However, a more recent study from France has suggested that the association of paediatric IBD with family history may in fact be stronger than previously appreciated, with a positive family history seen in 24% of paediatric cases compared with only 17% of adult cases in their study \((p = 0.05)\) (Pigneur et al., 2010), similar to our cohort observations. Issues related to accuracy in family history documentation by referring clinicians in the Barwon cohort may have further limited the significance of our current findings regarding family history in paediatric IBD. This reflects on the observational nature of the current study, with no direct patient contact possible to clarify points in the history that may have been lacking.

Overall, it is worth considering the wider implications of these local IBD rate results. Due to similarities in demographic features between the Barwon population and the broader population of Victoria and Australia, extrapolating data from the current study to these larger populations provides new incidence rate estimations for the broader Australian community. However, these estimation do not allow for the possible influence of longitude or latitude on IBD frequency, factors which have previously been implicated in IBD pathogenesis (Khalili et al., 2012). While acknowledging this possible limitation, Table 4.34 illustrates the estimated number of new IBD cases across Victoria and Australia during 2010-11.

<table>
<thead>
<tr>
<th></th>
<th>Estimated Victorian Incident IBD Cases</th>
<th>Estimated Australian Incident IBD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010-11</td>
<td>2010-11</td>
</tr>
<tr>
<td>Total IBD</td>
<td>1352</td>
<td>5440</td>
</tr>
<tr>
<td>CD</td>
<td>821</td>
<td>3304</td>
</tr>
<tr>
<td>UC</td>
<td>419</td>
<td>1686</td>
</tr>
<tr>
<td>IBDU</td>
<td>112</td>
<td>450</td>
</tr>
</tbody>
</table>

Table 4.34 IBD incident case projections for Victoria and Australia 2010-11.

Nationally, the diagnosis of over 5000 new cases of IBD each year represents a significant burden on health care resources. The cost associated with the diagnostic work-up of these cases alone would be high, as would the costs of therapy and hospitalisation for these patients. The cost in terms of the broader economic impact relating to IBD-related disability and impaired productivity should also be
considered. Further details on economic modelling and impact of IBD regionally and nationally will be discussed further at the end of Chapter 5, with reference to the results of the first prospective Australian IBD prevalence rate estimation study.

### 4.7 STRENGTHS/WEAKNESSES OF THIS STUDY

A number of factors relating to the design of this study can be considered to contribute to the reliability of the data produced regarding the revised local IBD incidence rate estimation. One of the main strengths of this current research is the prospective, population-based nature of the data collection, and the fact that cases were successfully captured from a wide range of referral sources. Over 60% of cases had multiple ascertainment sources, highlighting the success of the case capture-recapture methodology, reducing the chance of true incident cases being missed and increasing the sensitivity of the results.

In addition, case confirmation was prospective and clinically focused. Very strict diagnostic criteria were used in this study, ensuring improved specificity for a true diagnosis of IBD being included. After careful consideration, over 100 potential new IBD incident cases were excluded from the study because they did not strictly fulfil all diagnostic criteria. The clinically-orientated nature of the review process for potential new IBD referrals for the current study improves the specificity of the result.

There has been a tendency to rely on administrative coding or insurance data alone when previously assessing disease frequency estimation, with the associated potential bias that this brings. For example, Fonager et al published data on the assessment of the validity of cases coded in the Danish hospital information system in 1996 (Fonager et al., 1996). They found misclassification rates of 3% for CD, and 10% for UC when compared to traditional diagnostic criteria. More recent Danish research found a similar misclassification rate for UC of approximately 10% (Julsgaard et al., 2011). Furthermore, a study published in 2008 reviewed the reliability of diagnoses coded with the ICD-10 system (details of the ICD-10 are presented earlier in this chapter) (Stausberg et al., 2008). They found remarkably low rates of correct coding data entry, and cautioned against the extensive use of data derived purely from coding sources when assessing quality, health care financing ad disease assessment. These coding errors may have led to a significant over-estimation of rates in studies exclusively relying on this type of data.

The adherence to rigorous diagnostic criteria in the current Barwon study may have resulted in reduced sensitivity for case capture, as early or very mild cases of IBD that failed to fulfil all the required diagnostic criteria would have been excluded. This may have led to an underestimation of the true population incidence rate.

A number of important limitations in this study need to be considered. It remains difficult to assess the completeness of case ascertainment from the population. For instance, GP involvement in the capture of incident cases in the current study was low. Missing GP diagnosed IBD cases may have
underestimated the true population incident rate. Unfortunately, ethics permission was granted only for the release of de-identified details on possible cases from GP practices due to privacy legislation issues. This made the accurate assessment of potential new cases referred from GP sources challenging. In addition to the nature of data coming from GP’s, there remained a significant reluctance of GP’s across the region to volunteer patient data or become involved in the project. No new cases were independently referred by GP’s for consideration, despite multiple efforts to raise the profile of the research in the GP community.

The reluctance of GP participation in this project is likely multifactorial. One factor is likely to relate to concerns regarding privacy and confidentiality. There also appeared to be a general lack of interest in participating in research across most practices. This may be partly due to a lack of a ‘research-culture’ in general practice. Another important factor is likely to relate to time constraints and financial pressures facing GP’s working in primary practice, with an imperative to see large number of patients leaving little time for non-clinical, non-income producing activities, including research.

Another potential weakness of the current study related to the fact that the PI was removed from direct patient contact, again due to privacy issues and ethical constraints. This made assessment of a wide range of disease related factors challenging, requiring a reliance on the referring clinician’s history taking, investigation choices and documentation. This became a particular issue when considering descriptive features of the research relating to factors such as family history, smoking, and symptoms/signs at the time of IBD diagnosis. Direct contact with every patient would have ensured more complete and accurate recording of these descriptive factors.

Finally, the study population of Barwon is comparatively small when compared to some of the larger international studies in IBD epidemiology. Therefore the small cohort size certainly limited the analyses performed, with difficulty reaching statistical significance on many of the comparative calculations. Additionally, the time frame of 12 months is also relatively short, and may have negatively influenced the strength of the current study.

### 4.8 CONCLUSION/FUTURE DIRECTIONS

This study confirmed that incidence rates for IBD remain comparatively high in the Barwon region. While there has been some regional variation in rates and phenotypes when comparing the current cohort with the cohort from the same population studied in 2007-08, the overall figures suggest that the total incidence of IBD in Barwon has remained stable over the last 3 years.
The current study has re-established reliable research relationships with local clinicians and will provide the foundation to provide ongoing, routine, notification of incident IBD cases with the continual estimation of accurate, real-time loco-regional incidence data.

To overcome both the limitations related to the comparatively small sample size and issues relating to geographic rate fluctuations, future Australian IBD epidemiology research should focus on a wider collaboration between clinicians across different regions. This could include areas such as Tasmania, with its natural geographic isolation and contained health care system allowing reliable case capture. Ideally, this should ultimately be coordinated at a national level, in the form of a comprehensive Australia-wide IBD registry aiming for 100% case ascertainment rates. This concept of a national register will be further explored in chapter 6 of this research thesis. Future large-scale Australian collaborative projects would allow more reliable comparisons with similar internationally derived IBD incident cohorts, and would also allow further assessment into possible genetic and environmental influences on local IBD pathogenesis.
CHAPTER 5.

IBD PREVALENCE RATES AND DISEASE PHENOTYPES IN A REGIONAL AUSTRALIAN POPULATION.

5.1 BACKGROUND STATEMENT

Prevalence is a frequently used epidemiological term to describe how commonly a disease occurs within a population. Simply, the prevalence of a condition is calculated by dividing the number of known cases of a condition by the population at risk of the condition, and is usually expressed as a rate per 100,000 people (Webb et al., 2006). More specifically, point prevalence describes how many cases of a certain condition are in a particular population at a specific time.

An accurate understanding of disease prevalence, and of the patterns of disease regarding local phenotypes, is clinically useful. Prevalence rates allow physicians an understanding of the probability of the diagnosis of IBD in their local population. Prevalence data also provide a valuable insight into local disease burden, which is crucially important in the planning of health-care provision. Prevalence data are particularly relevant when considering chronic diseases, due to the accumulated disease burden from these conditions over time.

Globally, there has been a significant rise in IBD prevalence over the last 50 years, particularly in developed countries. More recently, IBD is emerging in regions where it was once considered rare, including South-East Asia. It is important to note that methodological heterogeneity has previously limited accurate comparisons between publications. Population-based prevalence studies have been undertaken in a number of countries in recent years. For example, a study from 2004 undertaken in Canterbury, New Zealand, reported local prevalence rates of 155 and 145 per 100,000 for CD and UC, respectively (Gearry et al., 2006). A review of US insurance claim records conducted between 2003-04 estimated prevalence rates for paediatric CD and UC of 43 and 28 per 100,000, and for adult CD and UC of 201 and 238 per 100,000, respectively (Kappelman et al., 2007). No prospective Australian population-based prevalence data is available for comparison. Currently published Australian estimates have been extrapolated from overseas data, based on the assumption that we share population similarities with the other Western cohorts.

There are a number of reasons why IBD prevalence rates are likely to be high in Australia. Firstly, recent population-based research suggests a high incidence rate for IBD in the local region (Wilson et al., 2010), a finding further supported by the results of the updated incidence study described in Chapter 4 of this thesis. In addition, IBD is commonly diagnosed at a young age and has little effect on mortality, further impacting on local prevalence rates.
Accurate local IBD prevalence estimates are important. Optimal IBD management requires early diagnosis and a multidisciplinary management approach. As IBD has no cure, therapy is required long-term, often at significant expense. IBD is also associated with significant impairment in health related quality of life (HRQOL) and high rates of disability, factors important to consider when assessing possible costs related to high IBD prevalence rates. IBD has also been associated with serious complications, including cancer development and the need for major surgery. An accurate understanding of disease prevalence thus allows adequate planning of health care resources to address all of these issues.

The best model of care for IBD requires a close collaboration between primary care providers and specialist gastroenterologists. However, it is not known how many IBD patients remain in long-term specialist care, or how many are ultimately managed in primary practice. This may have significant clinical implications regarding long-term disease maintenance, the ability to access new or improved therapeutics, and the prevention of IBD complications including colorectal cancer and osteoporosis. How many IBD cases that are managed by GP’s in Australia, without specialist gastroenterology input, is not known.

Considering all of these factors, it was considered important to undertake Australia’s first prospective population-based IBD prevalence study, and to also assess the burden of care seen in the primary care setting in our local region.

5.2 HYPOTHESIS

We hypothesised that the local IBD prevalence rates would be high when compared to methodologically similar international population-based results, and that the phenotypes would be similar.

Secondly, we hypothesised that a significant proportion of prevalent IBD cases would only be seen in primary care settings, representing a group of patients who may have delayed access to improved drug delivery systems, new therapeutics, and reduced surveillance for long term IBD related complications.
5.3 AIMS

1) To establish the first prospective Australian population-based IBD prevalence rate study to assess point prevalence at June 30\textsuperscript{th} 2011 in Barwon, Victoria.

2) To accurately assess local IBD-related burden by reviewing the duration of disease and IBD phenotypic details from within this local community.

3) To assess the proportion of IBD patients seen and managed through the primary care setting in the Barwon region.

5.4 METHODS

Details of the methodology chosen for this study are outlined in Chapter 3. Overall, the epidemiological methods used for prevalence rate assessment are the same as those used in the determination of local incidence rates, described in detail in Chapter 4 of this thesis.

There were, however, some important additional elements of data collection that were introduced for the prevalence study. Ethics and privacy constraints limited the detail of data that could be accessed when compared to the incidence study. A brief summary of the prevalence study methodology will be presented in the following paragraphs.

Data collection occurred over a 12 months period from July 1\textsuperscript{st} 2010 until June 30\textsuperscript{th} 2011. The population at risk was defined by the Barwon region in South West Victoria, Australia, with a population in 2011 of 293,246. The epidemiological method of case capture-recapture was again utilised for the prevalence study, with referrals originating from multiple sources as described previously. A summary of prevalent IBD case data sources is outlined in table 5.1.
Specific issues unique to the identification of prevalent IBD cases required additional data sources to be utilised. Australia operates a two tiered health-care system. Primary care is provided in the community by General Practitioners (GP), who manage a vast spectrum of acute and chronic medical conditions. The second level of care is provided by specialist doctors, access to whom generally requires referral from a GP. As IBD is a chronic, relapsing and remitting condition, many patients are likely to spend prolonged periods in remission. It was assumed that many clinically stable IBD patients may only be seen by their GP during these periods. Therefore, it was possible that these clinically stable cases may not be captured over the 12 month study period if data collection relied primarily on accessing specialist services or hospital level care. This would have lead to a significant under-estimation in true community IBD prevalence rates. Thus, when considering the IBD prevalence study, more extensive GP involvement was considered to be important.

281 GP’s were found to service the study area. To encourage involvement in the study, all GP’s were regularly contacted throughout the study period. This was initially via individual emails, and through the publication of articles relating to the project in the monthly regional GP Association (GPA) newsletter. Regular contact was also maintained with the educational support office of the GPA to raise the profile of the study. In addition, the author chaired an educational session for GP’s to raise awareness of IBD in general, and to promote the referral of cases to the study. The office managers of the largest 40 practices were then contacted, first via email, and then through telephone calls.
Depending on the practice response, the PI then attended consenting practices to interview GP’s and to manually perform GP patient record clinical database searches.

All GP practices maintained a current and comprehensive clinical database on patients attending their service, in line with recommendations by medical regulatory authorities. It was thus possible to search the records of active patients (those attending the service within the last 12 months) by key words, which included ‘IBD’, ‘Crohn’s disease’, ‘ulcerative colitis’, ‘Indeterminate colitis’ and ‘ulcerative proctitis’. Residential address was confirmed to be within the Barwon SD. Fully de-identified details were then released by the practice managers to the PI for inclusion in the prevalence study.

The level of diagnostic confirmation for prevalent cases varied depending on the referral source. Accurate diagnostic confirmation and phenotypic detail could be confirmed for all hospital-based prevalent case referrals, and also for cases that were initially referred as potential incident cases but were later found to be prevalent cases after review of medical records (details described in the incidence chapter of this thesis). However, the diagnosis of IBD in the case of de-identified referrals, where privacy concerns precluded the independent review of detailed clinical notes, relied on the referring clinician’s notes only. This was the case with all GP-sourced referrals. The de-identified clinical data that was requested on each potential prevalent case from these referring clinicians included;

1) patient initials
2) date of birth or age
3) gender
4) type of IBD and location
5) year of diagnosis
6) current postcode or suburb of residence
7) date last reviewed (to confirm still living in the area).

5.5 ETHICS APPROVAL

The study was conducted in accordance with the Helsinki Declaration. Ethics approval for this study was granted by the Barwon Health Human Ethics Research Committee, approval number 10/50. Due to the lack of direct patient contact and de-identified nature of the data that was stored, no prospective individual patient consent was deemed necessary.
5.6 DATA STORAGE/STATISTICAL ANALYSIS

Data was initially recorded manually. De-identified details on each case were then transferred to a specifically designed Excel spreadsheet. This was maintained on a secure, password-protected computer located in the Department of Gastroenterology of St Vincent’s Hospital, Melbourne.

Crude overall prevalence rates were calculated for total IBD cases, and separately for CD, UC and IBDU. Rates were expressed per 100,000 population. Age and gender standardised prevalence rates were then calculated using the direct method, based upon the World Health Organisation (WHO) standard population characteristics (http://meteor.aihw.gov.au/content/index.phtml/itemid/327276). This allowed valid comparisons to be made with other international cohorts. Rates were presented with 95% confidence intervals (CI) assuming a Poisson distribution. Any differences in descriptive data were assessed for significance using Chi-square tests or Fishers exact test where appropriate. A result of p < 0.05 was considered statistically significant.

5.7 RESULTS

5.7.1 IBD Prevalence Rates Barwon 2011-12

A total of 1011 prevalent IBD cases were identified during 12 months of data collection. This represented a crude total IBD point prevalence rate of 344.6 per 100,000 for the Barwon region on June 30th 2011. CD was the most common IBD sub-type identified. Further details are presented in tables 5.2 and 5.3. The majority of cases had IBD sub-types specified, with only 8 cases (0.7% of the cohort) being labelled as ‘type not specified’ (TNS).

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% total cohort)</td>
<td>579 (57%)</td>
<td>399 (39%)</td>
<td>25 (2.5%)</td>
</tr>
</tbody>
</table>

Table 5.2 Breakdown of prevalent cases by phenotype (excludes 8 cases where type of IBD was not specified).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Frequency</th>
<th>Crude prevalence rate</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>1011</td>
<td>100%</td>
<td>344.6/100,000</td>
<td>309.6 – 383.4/100,000</td>
</tr>
<tr>
<td>CD</td>
<td>579</td>
<td>57.3%</td>
<td>197.3/100,000</td>
<td>170.3 – 226.5/100,000</td>
</tr>
<tr>
<td>UC</td>
<td>399</td>
<td>39.5%</td>
<td>136/100,000</td>
<td>114.1 – 160.9/100,000</td>
</tr>
<tr>
<td>IBDU</td>
<td>25</td>
<td>2.5%</td>
<td>8.5/100,000</td>
<td>4.1 – 17.1/100,000</td>
</tr>
<tr>
<td>TNS</td>
<td>8</td>
<td>0.7%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.3 Barwon IBD point prevalence rates June 2011.
High IBD prevalence rates were demonstrated in the Barwon region, with tables 5.4 to 5.6 outlining age-specific and overall crude and age-standardised prevalence rates for CD, UC and IBDU.

### Table 5.4 Age-specific CD prevalence rates in Barwon in June 2011.

<table>
<thead>
<tr>
<th>Age Groups (years)</th>
<th>Crude CD prevalence rate</th>
<th>WHO age-standardised CD prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>19.7/100,000</td>
<td>19.1/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>190.7/100,000</td>
<td>192.2/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>296.1/100,000</td>
<td>300.9/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>187.9/100,000</td>
<td>188.5/100,000</td>
</tr>
<tr>
<td>65+</td>
<td>177.2/100,000</td>
<td>186.6/100,000</td>
</tr>
<tr>
<td>Total</td>
<td>197.3/100,000</td>
<td>190.5/100,000</td>
</tr>
</tbody>
</table>

### Table 5.5 Age-specific UC prevalence rates in Barwon in June 2011.

<table>
<thead>
<tr>
<th>Age Groups (years)</th>
<th>Crude UC prevalence rate</th>
<th>WHO age-standardised UC prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>10.7/100,000</td>
<td>10.5/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>58.3/100,000</td>
<td>58.5/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>136.8/100,000</td>
<td>165.8/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>204.5/100,000</td>
<td>205.0/100,000</td>
</tr>
<tr>
<td>65+</td>
<td>213.0/100,000</td>
<td>216.1/100,000</td>
</tr>
<tr>
<td>Total</td>
<td>136.0/100,000</td>
<td>114.8/100,000</td>
</tr>
</tbody>
</table>

### Table 5.6 Age-specific IBDU prevalence rates in Barwon in June 2011.

<table>
<thead>
<tr>
<th>Age Groups (years)</th>
<th>Crude IBDU prevalence rate</th>
<th>WHO age-standardised IBDU prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>3.6/100,000</td>
<td>3.4/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>5.3/100,000</td>
<td>5.2/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>11.2/100,000</td>
<td>10.1/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>2.8/100,000</td>
<td>2.9/100,000</td>
</tr>
<tr>
<td>65+</td>
<td>14.8/100,000</td>
<td>13.7/100,000</td>
</tr>
<tr>
<td>Total</td>
<td>8.5/100,000</td>
<td>7.3/100,000</td>
</tr>
</tbody>
</table>
The age range for the cohort was from 2-94 years, with a median age of 46 years. Age group specific crude and standardised prevalence rates are presented in Table 5.7.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Crude IBD prevalence rate</th>
<th>Age-standardised IBD prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>34.0/100,000</td>
<td>33.0/100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>254.2/100,000</td>
<td>256.0/100,000</td>
</tr>
<tr>
<td>25-54</td>
<td>482.0/100,000</td>
<td>482.6/100,000</td>
</tr>
<tr>
<td>55-64</td>
<td>395.1/100,000</td>
<td>396.4/100,000</td>
</tr>
<tr>
<td>65+</td>
<td>407.1/100,000</td>
<td>420.5/100,000</td>
</tr>
<tr>
<td>Total</td>
<td>344.6/100,000</td>
<td>315.2/100,000</td>
</tr>
</tbody>
</table>

Table 5.7 Crude and age-standardised IBD prevalence rates defined by age groups.

**5.7.2 Gender specific IBD Prevalence Rates.**

There was a slight overall female predominance in this cohort, with 568 females and 443 males. Overall, women had a higher IBD prevalence than men.

The total female population during the study period was 148,000. The age range for women was 2-93 years, with a median age of 44 years. Table 5.8 presents female IBD prevalence data.

<table>
<thead>
<tr>
<th>IBD</th>
<th>n</th>
<th>% of total women</th>
<th>Crude prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>568</td>
<td>100%</td>
<td>383.8/100,000</td>
</tr>
<tr>
<td>CD</td>
<td>330</td>
<td>58%</td>
<td>223.0/100,000</td>
</tr>
<tr>
<td>UC</td>
<td>223</td>
<td>39%</td>
<td>150.7/100,000</td>
</tr>
<tr>
<td>IBDU</td>
<td>12</td>
<td>2%</td>
<td>8.1/100,000</td>
</tr>
</tbody>
</table>

Table 5.8 Female IBD prevalence results for Barwon in June 2011.

The male population of Barwon during the period of study was estimated at 145,425. For men, the age ranged from 9-94 years, with a slightly older median age of 47 years compared to the female prevalent cases. Table 5.9 outlines male IBD prevalent data.
<table>
<thead>
<tr>
<th>IBD</th>
<th>n</th>
<th>% of total men</th>
<th>Crude prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>249</td>
<td>57%</td>
<td>171.2/100,000</td>
</tr>
<tr>
<td>UC</td>
<td>176</td>
<td>40%</td>
<td>121.0/100,000</td>
</tr>
<tr>
<td>IBDU</td>
<td>13</td>
<td>3%</td>
<td>8.9/100,000</td>
</tr>
</tbody>
</table>

Table 5.9 Male IBD prevalence results for Barwon in June 2011.

### 5.7.3 Phenotypes and Disease Duration Details.

Data regarding duration of disease were available on 444 cases, or 44% of the prevalent cohort. The median disease duration for all IBD was 7 years, with a range from 1-53 years. Comparative clinical data between CD, UC and IBDU are presented in table 5.10.

<table>
<thead>
<tr>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female cases</td>
<td>330 (57%)</td>
<td>223 (56%)</td>
</tr>
<tr>
<td>Male cases</td>
<td>249 (43%)</td>
<td>176 (44%)</td>
</tr>
<tr>
<td>Age range</td>
<td>5-94 years</td>
<td>2-93 years</td>
</tr>
<tr>
<td>Median age</td>
<td>42 years</td>
<td>51 years</td>
</tr>
<tr>
<td>Disease duration</td>
<td>7 years</td>
<td>7 years</td>
</tr>
</tbody>
</table>

Table 5.10 Clinical details of prevalent IBD subtypes.

### 5.7.4 Phenotype Sub-analysis.

350 prevalent CD cases had sub-phenotype data available for analysis (60% of the CD cohort). The perianal rate was 13%, while 70% of cases had ileo-colonic or colonic disease location. Further details of the CD cases are presented in Table 5.11.
<table>
<thead>
<tr>
<th>CD Localisation (Montreal)</th>
<th>Number of cases (n)</th>
<th>% of CD cohort with available sub-type data</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 (ileal)</td>
<td>102</td>
<td>29%</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>139</td>
<td>40%</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>104</td>
<td>30%</td>
</tr>
<tr>
<td>L4 * (isolation upper GI)</td>
<td>3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>L4 * (upper GI + L1 or L2)</td>
<td>26</td>
<td>7%</td>
</tr>
<tr>
<td>p * (isolated perianal)</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>p * (perianal + other location)</td>
<td>45</td>
<td>13%</td>
</tr>
</tbody>
</table>

Table 5.11 CD sub-phenotype disease location details for prevalent cases.

224 UC cases had sub-type data available for analysis (56% of the UC cohort). Details are outlined in Table 5.12, with an even distribution of disease location observed.

<table>
<thead>
<tr>
<th>UC Localisation (Montreal)</th>
<th>Number of cases (n)</th>
<th>% of UC cohort with available sub-type data</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 (proctitis)</td>
<td>76</td>
<td>33%</td>
</tr>
<tr>
<td>E2 (distal colitis)</td>
<td>74</td>
<td>33%</td>
</tr>
<tr>
<td>E3 (pancolonic)</td>
<td>74</td>
<td>33%</td>
</tr>
</tbody>
</table>

Table 5.12 UC sub-phenotype disease location details for prevalent cases.

5.7.5 Prevalence Data Source Analysis.

700 prevalent cases (69% of total) were identified from a single source, while the remaining 311 cases (31%) were identified from multiple different sources. Details of prevalent case sources are presented in tables 5.13.
Table 5.13 Analysis of prevalent IBD case data sources by number of sources.

<table>
<thead>
<tr>
<th>Number of data Sources</th>
<th>Cases</th>
<th>% of prevalent cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>700</td>
<td>69%</td>
</tr>
<tr>
<td>2</td>
<td>177</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>4%</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>1.3%</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Table 5.14 provides further details on prevalent case sources, defined as primary or secondary depending on where each case was first identified. Almost 60% were identified through the Geelong Hospital or local Gastroenterologist, however 30% were only seen in GP.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>Primary source</th>
<th>Secondary source</th>
<th>Total cases</th>
<th>% all referred cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterologist</td>
<td>407</td>
<td>75</td>
<td>482</td>
<td>31%</td>
</tr>
<tr>
<td>Geelong Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clinicians</td>
<td>69</td>
<td>39</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>- Coding database</td>
<td>42</td>
<td>113</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>- Pharmacy records</td>
<td>64</td>
<td>79</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>TOTAL Geelong Hospital</td>
<td>175</td>
<td>231</td>
<td>406</td>
<td>27%</td>
</tr>
<tr>
<td>Paediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Royal Children’s Hospital</td>
<td>26</td>
<td>7</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>- National paediatric database</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>- Geelong paediatricists</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>TOTAL Paediatric cases</td>
<td>33</td>
<td>22</td>
<td>55</td>
<td>4%</td>
</tr>
<tr>
<td>Endoscopy centres</td>
<td>9</td>
<td>3</td>
<td>12</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>St Vincent’s Hospital Melbourne</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Surgeons</td>
<td>5</td>
<td>25</td>
<td>30</td>
<td>2%</td>
</tr>
<tr>
<td>Pathology search</td>
<td>34</td>
<td>49</td>
<td>83</td>
<td>5%</td>
</tr>
<tr>
<td>General Practitioners</td>
<td>343</td>
<td>115</td>
<td>458</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>1011</td>
<td>522</td>
<td>1533</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 5.14 Prevalent IBD case source details.
5.7.6 Paediatric Prevalent Case Sub-Analysis (Age 19 and under).

There were 54 paediatric IBD cases identified, with CD being most frequently seen. The age range was 2-19 years, with a median age of 16 years. There were more male paediatric IBD patients than female (33 male versus 21 female). The median disease duration was 2 years (range 1-11 years). Table 5.15 presents IBD point prevalence rates (crude and age standardised) on June 30\textsuperscript{th} 2011 for the paediatric population in Barwon.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>% total</th>
<th>Crude prevalence rate</th>
<th>Age standardised prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD total</td>
<td>54</td>
<td>100%</td>
<td>71.6/100,000</td>
<td>53.2/100,000</td>
</tr>
<tr>
<td>CD</td>
<td>35</td>
<td>65%</td>
<td>46.4/100,000</td>
<td>34.5/100,000</td>
</tr>
<tr>
<td>UC</td>
<td>15</td>
<td>28%</td>
<td>19.9/100,000</td>
<td>14.8/100,000</td>
</tr>
<tr>
<td>IBDU</td>
<td>4</td>
<td>7%</td>
<td>5.3/100,000</td>
<td>3.9/100,000</td>
</tr>
</tbody>
</table>

Table 5.15 Paediatric IBD point prevalence rates for Barwon in June 2011.

Sub-phenotypic data was available on 35 paediatric cases (65% of the paediatric cohort). Table 5.16 presents details of disease location in prevalent paediatric cases based on the Montreal classification system, showing extensive disease location in paediatric UC cases and high rates of colonic involvement in paediatric CD cases were observed.
1. **CD Localisation**  
   (Total with available data = 26)  
<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 (ileal)</td>
<td>4</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>13</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>7</td>
</tr>
<tr>
<td>L4 *1 (isolation upper GI)</td>
<td>1</td>
</tr>
<tr>
<td>L4 *2 (upper GI + L1 or L2)</td>
<td>13</td>
</tr>
<tr>
<td>p *1 (isolated perianal)</td>
<td>1</td>
</tr>
<tr>
<td>p *2 (perianal + other location)</td>
<td>5</td>
</tr>
</tbody>
</table>

2. **UC Localisation**  
   (Total with available data = 9)  
<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 (proctitis)</td>
<td>1</td>
</tr>
<tr>
<td>E2 (distal colitis)</td>
<td>2</td>
</tr>
<tr>
<td>E3 (pancolitis)</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 5.16 Paediatric IBD prevalent case disease location details.

### 5.7.7 Prevalent cases of IBD in Primary Care.

Data was collected on 458 prevalent IBD cases seen in the primary care setting. Of these, 310 were only identified from GP searches. This equates to 31% of the total prevalent cohort being only seen in primary care during the 12 month study period. The remainder of prevalent cases identified from GP’s had been also been identified from other sources, and a further 19 cases were also identified from more than 1 GP practice, leaving a final GP IBD cohort of 439 individual cases (458 – 19 = 439). Details of these cases are provided in table 5.17.
### Primary Care IBD Sub-types and Gender Details

<table>
<thead>
<tr>
<th></th>
<th>Cases (n)</th>
<th>% of primary care IBD cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IBD</td>
<td>439</td>
<td>100%</td>
</tr>
<tr>
<td>CD</td>
<td>225</td>
<td>51%</td>
</tr>
<tr>
<td>UC</td>
<td>208</td>
<td>47%</td>
</tr>
<tr>
<td>IBDU</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>IBDTNS</td>
<td>4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Male</td>
<td>186</td>
<td>42%</td>
</tr>
<tr>
<td>Female</td>
<td>253</td>
<td>58%</td>
</tr>
</tbody>
</table>

### IBD Demographic Details

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>13-94 years</td>
</tr>
<tr>
<td>Median age</td>
<td>46 years</td>
</tr>
<tr>
<td>Disease duration (Median)</td>
<td>7 years</td>
</tr>
</tbody>
</table>

Table 5.17 Details of IBD cases seen in primary care settings in Barwon during 2010-2011.

GP response rates for study involvement were low. Despite multiple phone calls and emails to all GP practices in the region, only one practice initiated data collection independently, representing an initial GP response rate of 3%. Subsequently, a further 9 practices allowed the PI to attend their services and manually extract data from clinical practice software, bringing the number of GP practices included in data collection to 10. A total of 97 GP’s worked in these 10 practices, resulting in a final GP inclusion rate of 35% for the Barwon region.
5.8 DISCUSSION

The results of Australia’s first population-based IBD prevalence assessment confirm high rates of IBD in the local region, with crude IBD prevalence rates of 344.6 per 100,000. When standardised by age to allow valid international comparison, the local rate remained high at 315.2 per 100,000. CD was the most common subtype of IBD identified in this population (57.3%), followed by UC (39.5%). The frequency of IBDU in this population was 2.5%. Table 5.18 presents local and global comparative prevalence rate data.

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Region</th>
<th>Year Published</th>
<th>Date of Study</th>
<th>CD prevalence (per 100,000)</th>
<th>UC prevalence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobsen (Jacobsen et al., 2006)</td>
<td>Denmark</td>
<td>2006</td>
<td>2002</td>
<td>151</td>
<td>294</td>
</tr>
<tr>
<td>Bernstein (Bernstein et al., 2006)</td>
<td>Canada</td>
<td>2006</td>
<td>1998-2000</td>
<td>279</td>
<td>193</td>
</tr>
<tr>
<td>Loftus (Loftus et al., 2007)</td>
<td>Olmsted County, USA</td>
<td>2007</td>
<td>2001</td>
<td>214</td>
<td>214</td>
</tr>
<tr>
<td>Kappelman (Kappelman et al., 2007)</td>
<td>USA</td>
<td>2007</td>
<td>2003-04</td>
<td>201</td>
<td>238</td>
</tr>
<tr>
<td>Gearry (Gearry et al., 2006)</td>
<td>Canterbury, New Zealand</td>
<td>2006</td>
<td>2004</td>
<td>155</td>
<td>145</td>
</tr>
<tr>
<td>Studd</td>
<td>Barwon, Victoria, Australia</td>
<td>*</td>
<td>2010-11</td>
<td>197</td>
<td>136</td>
</tr>
</tbody>
</table>

Table 5.18 global IBD sub-type prevalence rate comparisons.

* Data yet to be published, n/a = not available.
Limited Australian data are available for comparison with the current IBD prevalence rate results. The small Australian study from NSW by Anseline et al published in 1988 showed a prevalence rate for CD of 34 per 100,000 (Anseline, 1995). By comparison, the current result of 197 per 100,000 suggests a significant rise in CD prevalence over the last 20 years. However, valid comparison between these studies is difficult, with the older results derived from hospital rather than population-based data.

When reviewing the international IBD prevalence literature, our results are comparable to those reported from the recent New Zealand cohort by Gearry et al in 2006 (please refer to table 5.18 above) (Gearry et al., 2006). While the Barwon cohort had a slightly higher total rate of CD (197 versus 155 per 100,000), and a slightly lower rate of UC (136 versus 145 per 100,000), the two populations both demonstrated a higher proportion of CD. While this observation has been reported in other international studies, including Canadian data by Bernstein et al, data from other areas suggest a different profile, with UC more commonly identified in some Western European populations (Jacobsen et al., 2006). The reason for this geographical difference is not known, but may relate to population genetic profiles or unique environmental factors.

Figure 5.1 outlines the local pattern of IBD prevalence rates across different age groups. The peak age of IBD prevalence in the Barwon region was between 25-54 years, with an age-standardised prevalence rate of 482.6 per 100,000. Overall, there was a general trend toward increasing prevalence through until age 55, with a relative plateau in rates observed over this age. Considering IBD sub-types independently, the younger peak in disease prevalence was apparent only for CD, with the highest disease prevalence seen in the 25-54 year age group. A similar observation was reported in Canadian population-based research (Bernstein et al., 2006). In contrast to CD, a gradual rise in UC prevalence with advancing age was observed in our population, with the highest prevalence rate noted in the over 65 year age group. A similar pattern was also recently described in North American populations (Kappelman et al., 2007). This may reflect on a more recent rise in CD incidence rates in the local population.
Overall, IBD was more common in women in the Barwon cohort (56% female versus 44% male). This was similar when considering both CD and UC populations separately. Loftus et al demonstrated a very similar result in a publication summarising several large North American studies, with the overall IBD frequency for women ranging from 48-60% (Loftus et al., 2002). Subsequent to this study, Kappelman et al published further North American IBD prevalence data, reporting specifically on gender distributions (Kappelman et al., 2007). These authors found that in adult patients, CD was slightly more common in women (OR 1.18), but was equally distributed across genders for UC. Bernstein et al demonstrated a similar pattern in Canada, where the female predominance was again most noticeable in CD patients with a female to male ratio of 1.3:1 (Bernstein et al., 2006).

The median age of the Barwon prevalent IBD cohort was 46 years. When examining the CD and UC populations separately, a difference in median ages became apparent, with UC patients being older (CD 42/UC 51 yrs). The small cohort of IBDU cases exhibited a similar age pattern to UC (median ages both 51 years), however a more even gender distribution was seen (52% male versus 48% female).

IBD phenotypes were defined using the Montreal classification system, details of which are described in chapter 2. However, restrictions in study design due to privacy issues meant that sub-phenotypic details were not available on all prevalent cases, and in those where data was available, the information was limited to disease location rather than behaviour. Disease location data was thus available in 60% of prevalent CD cases. This demonstrated that almost a third of prevalent CD cases had isolated ileal disease, a third had colonic disease, while 40% had an ileocolonic disease location. Upper GI involvement occurred in 7%, while 13% of the prevalent CD cohort had a history of perianal disease. Sub-phenotype details were only available on 56% of the prevalent UC cohort, representing a total of 224 patients. There was an even disease distribution across this cohort, with...
one third of cases each having proctitis, distal colitis and pancolonic disease. The distribution of disease was similar to that observed in the incident cohort described in the previous chapter.

A number of other IBD cohorts have described details of phenotypic distribution. For example, Ferrante et al found slightly different disease patterns in their Belgian cohort (Ferrante et al., 2007). They found proctitis in 22%, distal colitis in 37%, with more extensive disease most commonly seen in 41% of their UC cohort. They also had higher rates of perianal disease among their CD cohort (38%). Direct comparisons are difficult, as the Flemish cohort was not truly population-based. Any observed phenotypic differences may be explained by referral bias, with more severe and extensive IBD being seen in the specialized IBD clinic of Leuven University where their cohort was based.

When the working party responsible for the formulation of the Vienna classification system for CD published guidelines for describing disease location, they reported on a combined cohort of almost 800 CD cases from Denmark, Norway and the USA. In this cohort they found ileal location in 26.1%, colonic in 35.8%, ileocolonic in 33.3% and upper GI disease in 14.7% (Gasche et al., 2000). These results are very similar to our current Barwon results. Rates of perianal disease were not available for comparison with our current cohort.

Thia et al recently assessed disease distribution in a large population-based CD cohort from Minnesota in the USA (Thia et al., 2010). They documented a different pattern of disease than seen in the Barwon cohort. Of their 306 CD patients, ileal disease was most commonly seen at a rate of 45.1%, with colonic disease in 32% and ileocolonic disease in 18.6%. However the observed rates of upper GI disease (6%) and perianal involvement (17%) were very similar to the local results. Variability in defining L1 from L3 disease, particularly when the colonic disease is only limited to the caecum, may have been a factor. Although attempts are made to standardise CD classification using the Montreal system, there remains the possibility for variability in final interpretation of disease location. In addition, the Minnesota cohort was based on an inception population, with data gathered from the time of diagnosis. All cases were investigated extensively at diagnosis through a tertiary care centre, with all having dedicated small bowel assessments. During follow-up, only 6% of cases had an extension in disease location over a median follow-up of 8.4 years, although it is unclear from the study at what time point reassessment was made, and how extensive the reassessment was. In contrast, the Barwon prevalent cohort represents a single, observational cross-sectional assessment of local IBD, with no ability to assess details of how and at what stage of disease progress the phenotypes were determined. These factors impact on the ability to directly compare the two cohorts.

In general, the study of the epidemiology of paediatric IBD is challenging as IBD remains a rare diagnosis under the age of 11 years. Historical studies have often relied on very small case series, with large variations in the age limits used to define paediatric IBD (Lakatos, 2006). No Australian paediatric prevalence rate data have been previously published. Data on international paediatric IBD
rates are very limited. The current Barwon cohort therefore provides a valuable opportunity to observe contemporary and unique Australian paediatric IBD prevalence data derived from a true population-based setting, and further contributes to the international data in this area of IBD research.

A cohort of 54 cases aged 19 or younger were identified during the study period, representing a total crude paediatric IBD PR of 71.6 per 100,000 in the Barwon region. Similar to the adult population, CD was the dominant sub-type of IBD again seen, representing 65% of the paediatric cohort. This produced crude prevalence rates of 46.4 and 19.9 per 100,000 for CD and UC respectively. Table 5.19 presents data on international studies reporting WHO age-standardised paediatric IBD prevalence rates.

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Region</th>
<th>Year Published</th>
<th>Date of Study</th>
<th>CD prevalence rate (per 100,000)</th>
<th>UC prevalence rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein (Bernstein et al., 2006)</td>
<td>Canada</td>
<td>2006</td>
<td>1998-2000</td>
<td>32.2-71.1</td>
<td>17.5-30.7</td>
</tr>
<tr>
<td>Kappelman (Kappelman et al., 2007)</td>
<td>USA</td>
<td>2007</td>
<td>2003-04</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Studd Barwon, Australia</td>
<td></td>
<td>*</td>
<td>2010-11</td>
<td>34.5</td>
<td>14.8</td>
</tr>
</tbody>
</table>

* Not yet published

Table 5.19 Global paediatric IBD prevalence rate comparisons.

While the relatively small case numbers in our paediatric cohort may have limited the significance of cohort comparisons, a number of trends were apparent. Firstly, paediatric IBD in Barwon is more common in males (61% males versus 39% females). This male predominance in paediatric IBD has been previously described (Kappelman et al., 2007). Another observation from the Barwon prevalent paediatric cohort is the high rate of colonic disease location, independent of whether CD or UC was diagnosed. For example, in paediatric CD cases 50% had isolated colonic disease (compared with
40% of Barwon adult CD cases), while for UC panchonic disease was identified in 67% of cases (compared with 33% of Barwon adult UC cases). These observations have also been previously noted in larger population-based paediatric prevalent IBD cohorts (Kappelman et al., 2007, Bernstein et al., 2006). Furthermore, almost a quarter of paediatric CD cases had documented perianal disease, higher than the proportion observed in adults cases in the region, further reflecting on the more severe clinical phenotype of disease observed in children.

To improve the sensitivity of the final prevalence estimate it was important to maximise case ascertainment rates. This was achieved through the assessment of multiple data sources. Despite efforts to utilise this capture-recapture methodology, over 2/3 of cases were identified from a single source only. However, one third of cases were identified from more than one source, with up to 7 different sources in one instance. 310 IBD patients (31% of the entire prevalent cohort) were only identified from GP records. This suggests that almost one third of prevalent IBD cases are not under regular follow-up from a gastroenterologist, surgeon or paediatrician, suggesting a significant clinical load and responsibility for primary care providers. A recent study by Andrews et al found that of a large population of GP’s in South Australia, over one third of practitioners reported being uncomfortable with IBD management, particularly relating to the provision of maintenance therapy and the recognition and treatment of acute flares (Andrews, J. et al Article in press). When considering the burden of care demonstrated in the Barwon prevalent cohort, there is an urgent need for improved GP education regarding appropriate maintenance therapies, vaccination issues, cancer risk, osteoporosis assessment, nutritional and psychological problems, and the early recognition and management of IBD relapses.

In summary, this study has provided Australia’s first population-based IBD prevalence rates, and is therefore significant for several reasons. It demonstrates similarly high rates of IBD when compared to international data. It also allows a clearer understanding of the true local burden of disease, and should assist in planning adequate health-care for local IBD patients in the future. Furthermore, by extrapolating the local results to a state and national level, a wider appreciation of the true burden of IBD in Australia becomes apparent. Table 5.20 presents the population IBD prevalence estimates for Victorian and Australia, based on the new rates derived from the Barwon region.
<table>
<thead>
<tr>
<th>Disease Type</th>
<th>2010-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Barwon</td>
</tr>
<tr>
<td>CD</td>
<td>579</td>
</tr>
<tr>
<td>UC</td>
<td>399</td>
</tr>
<tr>
<td>IBDU</td>
<td>25</td>
</tr>
<tr>
<td>Total IBD*</td>
<td>1011</td>
</tr>
</tbody>
</table>

Table 5.20 Local IBD prevalence rates, with regional and Australia-wide IBD prevalence estimations.

* excludes “TNS” (type not specified) cases.

A recent publication from the USA reviewing the impact of IBD diagnosis on healthcare resource utilization should be considered in light of these revised Australian disease burden estimates. The study, based on administrative databases, found IBD patients had significantly increased rates of emergency department visits, endoscopy utilisation, outpatient clinic attendances and hospitalisation when compared to the background population (Kappelman et al., 2011). While it is difficult to predict the actual cost of providing this extra care to IBD patients, attempts have been made to quantify the amounts involved in their care. Using a Markov model analysis applied to the previously described Olmstead County CD population cohort, Silverstein et al estimated that the average CD patient would incur costs between $40,000 and $125,000 USD over the course of their illness (Silverstein et al., 1999). Importantly, these estimates are now over 12 years old. Many newer and potentially expensive therapeutic options are now available, including biological agents, with the consequence that the real costs are likely to be far higher. Economic modelling for IBD health care costs have previously been published for Australia. The Access Economics report from 2005, commissioned for the Australian Crohn’s and Colitis Association (ACCA), estimated the total economic burden of IBD in Australia for 2005 was $2.7 billion. If this cost model is now re-applied to the revised disease frequency estimates, IBD-related expenditure would have reached $3.4 billion in 2011, even excluding the impact of inflation.

5.9 STRENGTHS/WEAKNESSES OF STUDY

This current research provides the first prospective population-based IBD prevalence data for Australia. The strengths of the study relate to its prospective nature, and also to the extensive capture-recapture methodology utilized to maximize case ascertainment. The population-based nature of this research avoids many elements of bias encountered when epidemiological research is performed in a hospital-based setting. The extension of data capture into the primary care environment is a unique aspect of this current research for Australian IBD epidemiology, maximising IBD case identification and strengthening the validity of the final rate estimations.
A further strength of this research relates to the nature of the region studied. Barwon has clearly defined geographical boundaries, and the resident population is well characterised through reliable and accurate Australian census data. As defined previously, the local population demographics are also similar to the broader Victorian and Australian population, allowing a reliable extrapolation of disease prevalence rates outside the study region.

There are a number of areas of possible weakness identified from the current study, with potential to impact on the validity of the final prevalence rate figures. Firstly, ethics and privacy constraints limited the ability of researchers to accurately and clinically define each IBD case, or to compare the diagnosis of IBD against internationally recognised diagnostic criteria. While there was the opportunity for a rigorous clinical assessment of a subset of prevalent case records that were also identified through the incidence study described in Chapter 4 of this thesis, this level of case interrogation was not possible for all prevalent cases. Relying on the diagnosis of IBD from other clinicians may have over-estimated true prevalent cases through the inclusion of cases where a diagnosis of IBD would not have been present based on currently accepted diagnostic criteria (please refer to the diagnostic criteria descriptions in Chapter 2 of this thesis). The type of data collection allowed within the constraints of privacy and ethical considerations further limited the amount of disease-related information that could be accurately collected. For example, while it would have been valuable to collect information regarding disease diagnosis, rates of surgery and hospitalisation, disease activity, disease-related disability and health care associated cost, this was not possible within the design of the current project.

Another issue related to the low rates of GP involvement in prevalent case identification. Attempts were made to educate local GP’s regarding IBD, to raise awareness of the study and the local significance of results, and to minimise time and effort required by primary practitioners for case identification and notification. Despite this, there was a general reluctance and disinterest on behalf of GP’s to become involved in the research. The commonest reasons cited by primary practices and individual GP’s included a lack of time for research related activity, financial pressures, and concern regarding patient privacy and confidentiality. This remained an issue despite the data being in a de-identified format, and the project having full local ethics committee approval. It is likely this will have under-estimated the final prevalence rates by missing cases only seen in primary practice.

5.10 CONCLUSION AND FUTURE DIRECTIONS.

We have successfully produced the first population-based IBD prevalence data for Australia, demonstrating high rates of disease in our region, with figures greater than those previously estimated. Crohn’s disease is the most prevalent sub-type of IBD, representing a significant burden of care in both paediatric and adult populations.
Future IBD prevalence research in this region should remain population-based, however data collection needs to be further extended in several ways. More extensive GP involvement in data collection is vitally important. Prospective patient consent would allow far more extensive disease-specific data collection without concerns regarding privacy and confidentiality. To allow this increased level of data collection, more resources would be required, ideally allowing researchers to enter every GP practice across the region. To improve case diagnostic accuracy, more detailed clinical data would also be required.

One possible way of achieving this would be through the ongoing prospective enrolment of all patients with IBD in the Barwon region, whether incident or prevalent cases, in an extensive local IBD patient registry. This would require prospective collection of comprehensive disease-related information across the region. Not only would this allow real-time incidence and prevalence rate estimation, it would also allow disease progress assessments and disease evolution observations. Subsequent research collaboration, both nationally and internationally, could then facilitate the investigation into the effects of geography, climate, lifestyle and genetics on disease frequency and outcome. Further details regarding a population-based IBD registry are outlined in Chapter 6 of this thesis.
CHAPTER 6.

ESTABLISHING AUSTRALIA’S FIRST POPULATION-BASED IBD REGISTRY.

6.1 BACKGROUND STATEMENT.

IBD is a chronic condition, with a relapsing remitting course (Thoreson and Cullen, 2007). Many patients experience significant impairment to quality of life, and suffer significant disease-related disability (Andrews et al., 2010). Globally, there has been a dramatic increase in IBD frequency over the last 50 years (Baumgart et al., 2011). Recent local Australian data suggest high rates of IBD in our local region when compared to international estimates (Wilson et al., 2010). Despite significant advances in knowledge regarding many aspects of IBD, several key questions remain unanswered. For example, the aetiology of IBD is not yet known. It is also not clear why there are regional variations in IBD incidence and prevalence. While historical observations regarding the disease evolution of IBD have been published, the impact of improved diagnostic techniques and therapeutics on current IBD behaviour is not known.

Within Australia, there has been considerable recent interest in the establishment of a wide range of disease-specific registries, aimed at optimising the study of chronic diseases in the community. Examples of successful large-scale registries currently operational in Australia include the Victorian State Trauma Registry and the Australian Orthopaedic Association Joint Replacement Registry (Evans et al., 2011). The ultimate aim of these population-wide registries is to allow the accurate study of defined clinical outcomes, and to then subsequently allow clinicians to optimise patient care by comparison with published best-practice guidelines (Evans et al., 2011). However, in addition to these primary goals, a number of other epidemiological data can be derived from registries. For example, estimating prospective, real-time incidence and prevalence rates are possible. Observation of variations in disease patterns between age groups or regions may become clear. Registries can also provide a unique opportunity to explore disease aetiology and pathophysiology. And finally, by reviewing disease characteristics at time of diagnosis in those cases that reveal a complicated, aggressive disease course, clinicians may in future be able to target earlier and more aggressive therapies at this group of high risk patients.

Population-based IBD registries currently exist in a number of countries including Denmark, Norway and the USA (Molodecky et al., 2012). Unique observations have been derived from these cohorts, including assessment of rates of surgery and hospitalisation, in addition to patterns of medication use in newly diagnosed IBD patients. This has allowed the recognition of certain phenotypic features, including young age at onset and the presence of perianal disease, that are associated with a more
aggressive and complicated disease course (Walfish and Sachar, 2007). Furthermore, through genetic and serological studies of these cohorts, particular biological profiles have also been associated with a high risk of disease progression. For example, the genetic profile of CARD15/NOD2 in CD patients has been shown to predictive of ileal disease and earlier stricturing behaviour (Colombel, 2003). Serological markers including anti-IL12, anti-ompC, anti-CBir1 and ASCA have also been associated with earlier disease progression (Dubinsky et al., 2006).

There are currently no large scale population-based IBD registries in Australia. While a number of small, isolated patient databases exist, these are all based within hospital settings. One exception is the nation-wide Australian paediatric IBD registry. While this registry covers most states and has been collecting data for a number of years, the utility of this data is limited by the fact that it relies on only hospital-derived information, and is therefore not population-based. There is an urgent clinical and research need to establish a population-based, prospective IBD registry in Australia.

6.2 HYPOTHESIS

We hypothesised that the formation of a population-wide prospective pilot IBD registry in the Barwon region was technically feasible, and would allow unique IBD behaviour observations during the early stages of disease evolution in a community Australian setting.

6.3 AIM

1) To establish Australia’s first prospective, population-based IBD registry by collecting details on all confirmed incident IBD cases identified from within a geographically defined Australian population over a 12 month study period.

2) We aimed to demonstrate the success and utility of the new registry by assessing registry retention rates and important three-month clinical outcomes.

6.4 METHODS

The cases enrolled in the Barwon IBD registry were derived from the previously described incidence study outlined in Chapter 4 of this thesis. The methodology behind case ascertainment, IBD diagnostic criteria, and the level of clinical data collected has already been described, however a brief overview will be outlined below. Particular emphases on unique methodological features specific to registry formation have been made.
6.4.1 Study Population

The region chosen for this project was the population defined by the Barwon Statistical Division, in South-Western Victoria, Australia. The area had a population of just over 290,000 people in 2010/11, with details of the population demographics well established from accurate Australian census data. Please refer to Chapter 4 and 5 for further population details regarding total population size, socio-economic information and demographic details.

6.4.2 Case Definitions

To be considered for inclusion in the IBD registry, strict IBD diagnostic criteria had to be met. In addition, only cases of IBD diagnosed over the 12 month period from July 1st 2010 through until June 30th 2011 were considered for enrolment in the registry. Details of how the diagnosis of IBD was established and confirmed are outlined in Chapter 4 section 4.4.2.

6.4.3 Case Ascertainment

To establish a clinically meaningful clinical registry it was important to aim for high levels of case ascertainment across the population studied. The registry project relied on capturing potential new IBD cases from several sources, an epidemiological technique referred to as ‘capture-recapture’ methodology. This maximised case ascertainment rates, significantly reducing the chance of missing potential new cases of IBD in the region. While the local gastroenterologists and public hospital formed the core of case notification, a wide range of alternative data sources were also reviewed, details of which are outlined in Chapter 4 section 4.4.3.

6.4.4 Data Collection and Storage

To maintain the accuracy of data held within this registry, only basic epidemiological data was maintained in the registry. Details of the data collected and stored are outlined below in table 6.1.
<table>
<thead>
<tr>
<th>Registry ID number</th>
<th>First name</th>
<th>Surname</th>
<th>Medicare number</th>
<th>Medical record number</th>
<th>Date of birth (dd/mm/yy)</th>
<th>Gender</th>
<th>Referral source</th>
<th>Specialist (name and contact details)</th>
<th>General Practitioner (name and contact details)</th>
<th>Residential address</th>
<th>Home phone number</th>
<th>Mobile phone number</th>
<th>Date of diagnosis</th>
<th>Type of IBD (including phenotype)</th>
<th>Date of consent</th>
<th>Additional comments as needed</th>
</tr>
</thead>
</table>

**Table 6.1** Details collected on incident IBD cases for the Barwon IBD registry.

To assess the clinical utility of the registry, three-month clinical data was then collected on all new cases enrolled in the registry. This was achieved through contact with the patient's treating clinicians, medical note review, and by a review of relevant electronic databases including hospital coding, pathology, radiology and pharmacy records. Details of the outcome data that were reviewed are further outlined in table 6.2.
Table 6.2 Three month clinical data reviewed from cases enrolled in the Barwon IBD registry.

For the purpose of the pilot registry, fully identifiable demographic details were maintained. These were kept on a secure, password-protected computer, on a purpose-designed Excel spreadsheet. Data was entered after the consent process was completed, details of which are explained below in section 6.5. Data was initially collected manually, and final registry data-fields were entered electronically into the registry by the PI only. Quality control of data was then assessed by a second review of all registry data-fields three months after the initial formation. Any demographic or clinical discrepancies were then clarified again with the treating clinician before details were included in the finalised pilot IBD registry.

### 6.4.5 Statistical analysis

Registry enrolment rates were assessed. Rates of medication use, surgery and hospitalisation were assessed across the registry participants. Changes in disease location and behaviour 3 months from initial diagnosis were also assessed. Comparative analyses of disease features, treatments and complications were performed between different IBD phenotypes, for specific age groups and by gender by using a series of chi-square analyses. A result of $p < 0.05$ was considered statistically significant. When assessing factors that might predict the need for different treatment types, binary logistic regression analysis was performed, with results expressed as odds ratios with 95% confidence intervals, and subsequent $p$ values.
6.5 ETHICS APPROVAL AND CONSENT

Ethics approval for this Pilot IBD Registry was granted by the local Barwon Research and Ethics Committee. The approval number for this project was 10-51.

The technique of opt-out consent was used for participant inclusion in the pilot registry. After clinical confirmation of a new diagnosis of IBD, all potential registry participants were sent a letter detailing information on the registry, the nature of the data being collected, how it was to be maintained, and what the purpose of the pilot registry was. Detailed study contact information was also provided. Details of the consent form can be found in Appendix 4. Consent was then inferred if the patient did not contact the study team to request that their details were not to be maintained in the registry. This technique of opt-out consent has a strong precedent in epidemiological research, having been widely used to populate disease registries in the past. Opt-out consent has many advantages over the traditional opt-in consent processes, including improved case retention rates. Further details regarding the opt-out consent process and why it was chosen for this project will be presented later in this chapter in section 6.7.

6.6 RESULTS

6.6.1 Retention Rates, IBD Phenotypes and Disease Severity.

During the 12 month study period from July 2010 until June 2011, a total of 71 new cases of IBD were identified across the Barwon region. All new cases were successfully recruited into the pilot registry using the opt-out consent process (100% retention rate), with no patient electing to withdraw from registry participation. During the short 3 month follow-up period of the current study, 3 patients had a change of disease phenotype recorded. Details of these changes are presented in table 6.3.

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical details</th>
<th>Initial phenotype</th>
<th>Revised phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>15 yo male</td>
<td>UC (E3)</td>
<td>IBDU</td>
</tr>
<tr>
<td>Case 2</td>
<td>39 yo male</td>
<td>CD (A2L2B1)</td>
<td>IBDU</td>
</tr>
<tr>
<td>Case 3</td>
<td>14 yo female</td>
<td>IBDU</td>
<td>UC (E3)</td>
</tr>
</tbody>
</table>

Table 6.3 Changes to IBD phenotype three months from initial diagnosis.

The description of final disease phenotypes included in the Barwon IBD registry is presented in table 6.4.
A clinical assessment of severity was made by most treating gastroenterologists (94.5% of cases), details of which are presented in table 6.5.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Cases</th>
<th>% of registry cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>34</td>
<td>47.9%</td>
</tr>
<tr>
<td>Mild-Moderate</td>
<td>9</td>
<td>12.7%</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>12.7%</td>
</tr>
<tr>
<td>Moderate-severe</td>
<td>13</td>
<td>18.3%</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>2.8%</td>
</tr>
<tr>
<td>Not documented</td>
<td>4</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

Table 6.5 Clinician-based IBD severity assessment.

### 6.6.2 Hospitalisation Rates.

Twenty patients required a total of 29 hospital admissions within the first three months from IBD diagnosis, resulting in a three month hospitalisation rate of 28% for all registry participants. This excluded the index endoscopy that resulted in the initial diagnosis of IBD, unless the patient had already required hospital inpatient admission. Reasons for subsequent hospitalisations included diagnostic work-up, the need for emergency surgical procedures, inpatient endoscopies and iron infusions, small bowel obstruction and the need for intravenous steroids at the time of diagnosis.

### 6.6.3 Need for Surgery.

Eight patients required surgery within three months of IBD diagnosis, representing a surgical rate of 11%. Surgery occurred only in CD patients. Of those needing surgery, an average of 1.5 operations
were performed (range 1-3). Only one case required intestinal resection, with most surgery relating to perianal disease. Details of surgery are presented in table 6.6.

<table>
<thead>
<tr>
<th>Case details</th>
<th>IBD type</th>
<th>Phenotype</th>
<th>Number of operations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 yo female</td>
<td>CD</td>
<td>A1L3pB1</td>
<td>1</td>
<td>EUA and drainage perianal abscess</td>
</tr>
<tr>
<td>26 yo male</td>
<td>CD</td>
<td>A2L3p(+L4)B1</td>
<td>1</td>
<td>EUA and drainage perianal abscess</td>
</tr>
<tr>
<td>19 yo female</td>
<td>CD</td>
<td>A2L3pB1</td>
<td>3</td>
<td>EUA with drainage, EUA with seton insertion, EUA</td>
</tr>
<tr>
<td>20 yo female</td>
<td>CD</td>
<td>A2L3B1</td>
<td>1</td>
<td>Diagnostic laparoscopy</td>
</tr>
<tr>
<td>19 yo female</td>
<td>CD</td>
<td>A2L1B3</td>
<td>2</td>
<td>Ileocolic resection for free perforation and ileovesical fistula, stoma revision for parastomal herniation</td>
</tr>
<tr>
<td>36 yo male</td>
<td>CD</td>
<td>A2L3pB2</td>
<td>1</td>
<td>EUA and skin tag excision</td>
</tr>
<tr>
<td>31 yo female</td>
<td>CD</td>
<td>A3L1B2</td>
<td>1</td>
<td>Diagnostic laparoscopy</td>
</tr>
<tr>
<td>51 yo male</td>
<td>CD</td>
<td>A3L2pB1</td>
<td>1</td>
<td>EUA with sphincterotomy and anal dilatation</td>
</tr>
</tbody>
</table>

Table 6.6 Details of surgery required within three months of diagnosis.

Tables 6.7 and 6.8 compare features of IBD patients requiring early surgery with the remainder of the registry participants, with CD patients statistically more likely to require surgery 3 months from diagnosis, particularly in the presence of perianal disease.

<table>
<thead>
<tr>
<th></th>
<th>With surgery n = 8</th>
<th>Without surgery n = 63</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% male</td>
<td>50%</td>
<td>49%</td>
<td>0.339</td>
</tr>
<tr>
<td>Median age</td>
<td>31</td>
<td>38</td>
<td>0.804</td>
</tr>
<tr>
<td>CD</td>
<td>8 (100%)</td>
<td>35 (56%)</td>
<td>0.014</td>
</tr>
<tr>
<td>UC</td>
<td>0</td>
<td>22 (35%)</td>
<td>0.042</td>
</tr>
<tr>
<td>IBDU</td>
<td>0</td>
<td>6 (9%)</td>
<td>0.474</td>
</tr>
</tbody>
</table>

Table 6.7 Impact of gender, age and IBD subtype on need for surgery.
### 6.6.4 Medication Use Three Months from IBD Diagnosis.

#### Antibiotics.

Antibiotics were prescribed for 6 cases of newly diagnosed IBD (8% of cohort). All were diagnosed with CD, and 4 of these had active perianal disease. Antibiotics used included metronidazole (3 cases), ciprofloxacin and metronidazole combination (2 cases), and Augmentin Duo Forte (1 case).

#### Sulfasalazine/5-ASA Agents.

Fifty patients were commenced on either sulfasalazine or an alternative oral 5-ASA agent within three months from diagnosis, representing 70% of the total cohort. Of those starting any oral 5-ASA agent, 6 had a diagnosis of IBDU (100% of IBDU cases), 14 had UC (64% of UC cases), and 30 had CD (70% of all CD cases).

27 patients commenced therapy with sulfasalazine, with 9 developing intolerance within 3 months requiring a switch to another 5-ASA (30% intolerance rate). Of the 18 patients who continued sulfasalazine for 3 months, the dose ranged from 1-4g per day.

---

#### Table 6.8 Impact of disease phenotype on need for surgery.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>With surgery</th>
<th>Without surgery</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 8</td>
<td>N = 63</td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>2</td>
<td>11</td>
<td>0.542</td>
</tr>
<tr>
<td>L2</td>
<td>1</td>
<td>10</td>
<td>0.328</td>
</tr>
<tr>
<td>L3</td>
<td>5</td>
<td>15</td>
<td>0.223</td>
</tr>
<tr>
<td>L4</td>
<td>5</td>
<td>33</td>
<td>0.037</td>
</tr>
<tr>
<td>L5</td>
<td>2</td>
<td>2</td>
<td>0.151</td>
</tr>
<tr>
<td>L6</td>
<td>1</td>
<td>0</td>
<td>0.186</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>5</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

---

**Table 6.8** Impact of disease phenotype on need for surgery.
In this registry cohort, 23 IBD patients started therapy with mesalazine instead of sulfasalazine due to documentation of previously established sulphur intolerance or allergy. None of these patients subsequently experienced side effects relating to 5-ASA, although 2 patients ceased therapy due to lack of efficacy.

Table 6.9 outlines phenotypes associated with oral 5-ASA prescription. More extensive colonic disease (either E3 for UC or L2 for CD) was associated with more frequent use of oral 5-ASA agents, although this failed to reach statistical significance (p=0.27 for CD and p=0.14 for UC when comparing rates of oral 5-ASA use in limited disease with more extensive disease location).

<table>
<thead>
<tr>
<th>IBD Phenotype</th>
<th>Total in registry</th>
<th>Total treated with oral sulfasalazine or other 5-ASA</th>
<th>% of phenotype-specific cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>13</td>
<td>7</td>
<td>54%</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>11</td>
<td>10</td>
<td>91%</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>19</td>
<td>14</td>
<td>74%</td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1 (proctitis)</td>
<td>7</td>
<td>2</td>
<td>29%</td>
</tr>
<tr>
<td>E2 (distal colitis)</td>
<td>6</td>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>E3 (pancolitis)</td>
<td>9</td>
<td>9</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 6.9 Impact of phenotype on aminosalicylate prescription.

Topical 5-ASA was prescribed to 9 patients (13% total registry). Of these, 8 had UC and 1 had CD. Within UC, topical therapy was associated with more distal disease location (E1 proctitis 5 cases, E2 distal colitis 1 case, E3 pancolitis 2 cases). A combination of suppositories and enemas were prescribed. Although suppositories were only prescribed in UC for proctitis, two further patients with limited rectal disease received an enema formulation of 5-ASA.

Finally, a combination of oral and top 5-ASA/sulfasalazine was prescribed to three patients. All had UC, and had extensive, pancolonic disease.
Corticosteroids.

9 patients received inpatient admission for intravenous hydrocortisone within three months of diagnosis (22% of cohort). All received a dose of 100mg four times per day. Three of these patients ultimately required surgery, although none required intestinal resection. Table 6.10 outlines the clinical details of those requiring intravenous steroid therapy soon after diagnosis, with trends toward younger age, female gender and more extensive disease predicting need for intravenous steroids.

<table>
<thead>
<tr>
<th></th>
<th>Intravenous steroids</th>
<th></th>
<th>No intravenous steroids</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Total n = 9</td>
<td>% of total steroid receiving cohort (phenotype percentages expressed per IBD subtype numbers)</td>
<td>Cases Total n = 62</td>
<td>% total cohort not receiving steroid (phenotype percentages expressed per IBD subtype numbers)</td>
</tr>
<tr>
<td>Median age</td>
<td>20 years</td>
<td>-</td>
<td>39 years</td>
<td>-</td>
</tr>
<tr>
<td>Females</td>
<td>6</td>
<td>67%</td>
<td>30</td>
<td>48%</td>
</tr>
<tr>
<td>IBD phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>4</td>
<td>44%</td>
<td>39</td>
<td>63%</td>
</tr>
<tr>
<td>L1</td>
<td>0</td>
<td>-</td>
<td>13</td>
<td>33%</td>
</tr>
<tr>
<td>L2</td>
<td>1</td>
<td>25%</td>
<td>10</td>
<td>23%</td>
</tr>
<tr>
<td>L3</td>
<td>3</td>
<td>75%</td>
<td>16</td>
<td>44%</td>
</tr>
<tr>
<td>UC</td>
<td>4</td>
<td>44%</td>
<td>18</td>
<td>29%</td>
</tr>
<tr>
<td>E1</td>
<td>0</td>
<td>-</td>
<td>7</td>
<td>39%</td>
</tr>
<tr>
<td>E2</td>
<td>1</td>
<td>25%</td>
<td>5</td>
<td>28%</td>
</tr>
<tr>
<td>E3</td>
<td>3</td>
<td>75%</td>
<td>6</td>
<td>33%</td>
</tr>
<tr>
<td>IBDU</td>
<td>1</td>
<td>12%</td>
<td>5</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 6.10 Clinical characteristics stratified by need for intravenous steroids
However, logistic regression analysis revealed that the initial clinician’s assessment of disease severity was the only factor that accurately predicted the need for intravenous steroid, as outlined in Table 6.11.

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Result (Odds ratio OR, confidence interval CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>OR 0.968 (95% CI 0.924-1.012, p=0.170)</td>
</tr>
<tr>
<td>Gender</td>
<td>OR 2.133 (95% CI 0.489-9.303, p=0.313)</td>
</tr>
<tr>
<td>(Male: Female)</td>
<td></td>
</tr>
<tr>
<td>IBD Type</td>
<td>OR 2.17 (95% CI 0.486-9.654, p=0.310)</td>
</tr>
<tr>
<td>(CD versus UC)</td>
<td></td>
</tr>
<tr>
<td>Family history of IBD</td>
<td>OR 1.533 (95% CI 0.269-8.739, p=0.630)</td>
</tr>
<tr>
<td>Severity assessment</td>
<td>OR 2.573 (95% CI 1.391-4.757, p=0.003)</td>
</tr>
</tbody>
</table>

Table 6.11 Logistic regression analysis assessing predictors of need for intravenous steroid at IBD diagnosis.

Forty two patients were commenced on oral corticosteroids during the first three months from diagnosis, a steroid use rate of 59% across the registry. One patient received Budesonide, whilst the remainder received prednisolone. In total, 55% of the UC cohort required oral steroids, 63% of the CD cohort, and 50% of the IBDU cohort.

A total of 15 patients (21%) remained on steroids three months from diagnosis. Of these 15 patients, 9 commenced 5-ASA therapy, 5 started an immunosuppressive agent, and one received a combination of immunosuppressive with 5-ASA. No steroid dependent patients received biological therapy within three months from diagnosis.

Topical steroids were used in 5 patients, including three UC patients with distal disease, and two CD patients with distal colonic activity.
Immunomodulators.

Immunosuppressive therapy was commenced in 8 patients within three months from IBD diagnosis (11% of entire cohort). All had CD (5 ileocolonic, 1 colonic, 2 ileal, and 2 had additional perianal disease). The median age of those requiring immunosuppressive therapy was 19.5 years, compared to those patients not requiring immunosuppression of 39 years. Slightly more women required immune suppression than men (Female 55%, male 45%). None of these differences reached statistical significance.

All cases receiving an immunosuppressive were initially commenced on Azathioprine, however two patients (25%) ceased therapy due to side effects (nausea/abnormal liver function). One case successfully changed to 6-Mercaptopurine (6MP), while the other commenced subcutaneous Methotrexate therapy.

For Azathioprine the starting dose ranged from 50 – 150mg daily. All cases had dose escalation within three months, with those 6 patients that remained on Azathioprine at three months receiving 75-200mg daily. No infection related events were recorded in these patients. TPMT activity assessment was not routinely documented or recorded.

Of the eight cases receiving immune suppression at the end of three months, three were considered in clinical remission by their treating clinician, one had no data regarding disease activity available, and four cases had ongoing active disease requiring steroid use. No cases required salvage cyclosporine therapy during the three months from diagnosis.

Biological Agents.

No patient in the registry received a biologic agent within 3 months from IBD diagnosis.

Additional Data Regarding Therapy.

As this study was performed within a ‘real-world’ community environment, it allowed a unique insight into the practicality of managing newly diagnosed IBD patients outside specialist-referral hospital centres. For example, after three months from diagnosis, three patients were lost to medical follow-up with serial non-attendance at specialist and GP rooms (4% of initial cohort).

One CD patient became pregnant during follow-up, after her disease was controlled with immunosuppressive therapy (Azathioprine). 19 cases were clinically assessed as having active disease at the end of three months from diagnosis (27%), 12 were inactive (17%), whilst no data on
Disease activity was available for the remaining 40 patients (56%). In 7 cases (10%), step-up therapy (with either 5-ASA or immunomodulators) was commenced just after the three-month follow-up mark, with a further 8 cases requiring additional courses of systemic steroids (11%). One patient had an application for a biological agent to start after three months of therapy with steroids and immunomodulator therapy. One further late adverse reaction to sulfasalazine was documented, requiring cessation of this medication.

6.7 DISCUSSION

We successfully demonstrated that it is feasible to establish a high quality, prospective, population-based IBD registry in a regional Australian setting. The methodology used to identify potential patients, to maximise case ascertainment rates across the region, and to ensure a high specificity for an accurate diagnosis of IBD, is based on a number of sound epidemiological principles. By adhering to these principles, we have maximised the quality and consistency of the data maintained within this registry. Longitudinal observation of this inception cohort has allowed important short-term disease related outcomes to be accurately assessed, supporting the validity of the registry, and demonstrating its clinical utility.

The rationale for choosing the design of the pilot registry will be discussed in section 6.7.1. Details of how this pilot project could be expanded in the future to incorporate a more widely accepted and clinically useful registry are also discussed. Section 6.7.2 will detail the clinically significant disease outcome data that was collected from this pilot registry cohort. This will include comparisons with other population-based inception cohort internationally, in addition to comparing the observed patterns of real-world community practice-based therapy with current IBD therapeutic guidelines. To conclude the chapter, future plans for this registry will be discussed, including plans for international collaboration with a number of IBD epidemiology consortia, and the planning of a case-matched observational study between the Barwon cohort and a similarly derived Danish IBD inception cohort.

6.7.1 Modelling for a community-based clinical IBD Registry

Disease-specific clinical registries have an established role in the long term study of chronic diseases, and assist in ensuring the delivery of high quality and cost-effective health care (Evans et al., 2011). The usefulness of any disease registry is directly related to the quality of the data that is maintained. This, in turn, relies on ensuring that epidemiologically high quality information is initially collected, is then stored in a readily accessible way, and is reliably maintained with regard to data quality control and information security (Evans et al., 2011, Evans and al, 2011, Burisch et al., 2011). These principals have all been practically applied to this pilot IBD registry project.
To maximise the initial quality of the data being entered, clear, uniform and well-defined criteria for inclusion into the registry were established. By adhering to strict clinical and validated IBD diagnostic criteria, standardisation of entry into the registry was achieved. In addition, by recording limited, simple, disease-specific and demographic details, the risk of unreliable or poor quality data being included into the registry was significantly reduced (Evans and al, 2011). This also simplified and streamlined the process of registry enrolment, improving access to the registry and increasing the registry’s practicality. While this may not be a major issue in the purely research environment of the current pilot registry, it is an important factor to consider when planning for the creation of an ongoing community-based registry which would rely heavily on practicing clinicians entering patient details, without the luxury of dedicated research staff. For these reasons, the simple demographic and disease details outlined in Table 6.1 in the methodology section of this chapter were chosen to populate the pilot registry.

A further benefit of the model used for this pilot registry was that community-based clinicians only needed to be involved in the initial identification of new cases, with the PI collecting all subsequent relevant clinical information, confirming the diagnosis of IBD, standardising data collection, completing final data entry and subsequent quality control measures. Any disease-related observations then relied on the extraction of data from a variety of sources using the demographic details maintained in the registry, details of which have been previously discussed. However, for future research, a number of other data collection tools could be used. For example, direct patient contact could be made through questionnaires or interviews. Prospective review of hospital records, or medication tracking via the use of unique Medicare numbers, could be performed. These future projects would be subject to relevant ethics approval. The major benefit of this model of registry is that it greatly reduces any time burden on busy community-based clinicians, a factor very important in the real-world clinical environment where significant time and financial pressures exist.

An alternative registry model involves far more in depth data collection at the time of registry enrolment, followed by prospective disease-related outcome updates entered by the treating clinician. This may include more detailed demographic data, and personal background information allowing for the assessment of disease risk factors. Clinical data and outcomes may include data on hospitalisation rates, surgery and medication use. This second registry model has a number of benefits (Evans and al, 2011, Bufalino et al., 2011). However, while it allows for easier and more extensive data extraction to occur without specific patient contact, it relies very heavily on ongoing and regular clinician input. Collecting an increased number of data points also makes it harder to maintain the quality of the data in the registry. Despite these challenges, this latter model has been favoured by the recently created web-based epidemiological database for IBD in Europe, the Epicom study (Burisch et al., 2011).

Consent for inclusion into most clinical registries can take two main forms. Opt-in consent requires the patient to sign a consent form at entry into the registry. This is labour and cost intensive, and has been traditionally associated with low retention rates (Evans et al., 2011). The alternate method of
consent, and the one chosen for the majority of clinical registries operating in Australia, is the opt-out consent process. This involves sending details of the registry to possible participants, and inferring consent if patients do not request that their details are not maintained in the registry. This was the consent chosen for the Barwon pilot IBD registry, and resulted in a 100% case inclusion rate. While a number of patients in the pilot registry did contact the PI after receiving the consent information in the mail, none wanted to withdraw from the registry, with all patients expressing their support and enthusiasm for the project.

For the purpose of this research project to create a community-based IBD registry, it was not necessary to consider issues relating to the widespread accessibility of the registry, or cost. These factors are, however, vitally important to consider when attempting to translate the current small pilot registry into a model that would be practical as a clinically useful community-based IBD registry.

Regarding the accessibility of the data held in the pilot registry, maintaining the registry on a secure, password protected computer in a simple Excel spreadsheet format was sufficient for the purpose of this initial project. In addition, the manual collection of health-related information and subsequent data entry by the PI was feasible. This model would not be appropriate when planning for a longer term, community-based registry. Clinicians would need to access the registry prospectively, and would have only limited time available for data collection and entry. Moving to a web-based epidemiological database, with multi-site access into a highly secure registry, would be a more appropriate model (Burisch et al., 2011). Linking the registry with existing electronic datasets would also be advantageous, as real-time updates relating to admissions, complications, medications dispensed and investigations would be possible. The disadvantage of this format for registry development is largely based on associated costs.

Finally, when considering cost associated with clinical registries, is important to consider financial implications involved with data collection, data entry, registry maintenance, analysis and registry security (Bufalino et al., 2011). This is a particularly important issue in resource-limited areas and the current era of health-care expenditure constraints (Safavi et al., 2010). Ideally, proving the cost-effectiveness of the registry may secure the required funding, however this is often difficult to achieve (Evans et al., 2011). Registry funding can come from a variety of sources, including private business, pharmaceutical companies, governmental agencies, hospitals and charities. Ethical consideration needs to be given to funding sources, with potential implications on data ownership and conflict of interest. Funding through non-business sources is the most ethically sound source, with some funding available through the recently established Australian Commission for Safety and Quality in Health Care. Collaboration with the Australian Crohn’s and Colitis Association would potentially be beneficial with regard to financial support for a new population-wide IBD registry in Australia.
6.7.2 Three Month Outcome Data from a Population-Based IBD Registry.

As previously outlined, a knowledge of patient factors that could assist the clinician in predicting which new IBD patients are at risk of severe disease is highly desirable. Information of this nature is best derived from longitudinal observational epidemiology, providing disease behavioural observations that can be compared with different phenotype details at disease onset. Observations on disease course that are hospital-based are open to referral bias, and are thus less widely applicable to populations outside the hospital setting. A more reliable indication of true disease evolution comes from longitudinal observations from population-based cohorts.

Important markers of disease outcome in IBD include rates of surgery and hospitalisation (Kamm, 2011). In addition, both these factors have significant health-related cost implications. It was possible to assess both hospitalisation and surgical rates from the current Barwon IBD registry participants. Just under one third (28%) of the current cohort required at least one hospital admission within three months of diagnosis. This excluded hospital stays regarding the index endoscopy, which was usually done as a day-admission. There is little published data regarding very early rates of hospitalisation available for comparison. Bernstein et al published hospitalisation rates from a population-based Canadian IBD cohort, revealing rates of over 20% per year (Bernstein et al., 2006). However, these rates were based on 5 years of observation, not just rates around the time of diagnosis. Similarly a number of other publications have documented longer term trends in hospitalisation rates, but none have specified rates for within the first three months from diagnosis (Kugathasan et al., 2003, Bewtra et al., 2007).

We demonstrated that within the first three months of diagnosis the surgical rate was 11%, and surgery was only performed on patients with CD. This observation was statistically significant, despite the relatively small sample size. No patient diagnosed with UC during the study period presented with fulminant disease that did not respond to steroid therapy, hence no colectomy was required within the first three months of diagnosis. Eight CD patients required a total of 11 operations within three months of diagnosis, representing a surgical rate among newly diagnosed CD patients of 19%. Patients with perianal disease were over-represented in the group requiring surgery (5 of the 8 patients), with the majority of the procedures relating to examination under anaesthesia, abscess drainage and seton drain insertions. Two CD patients underwent diagnostic laparoscopies, while one CD patient with penetrating disease at presentation required significant intestinal resection at the time of diagnosis. While a trend toward younger age and a greater risk of early surgery was observed, this failed to reach statistical significance.

As with data regarding hospital rates, there is a lack of published literature regarding very early surgical rates in IBD. In fact, there are no publications only restricted to outcomes within three months of diagnosis. In a review of a population-based Danish cohort, Vind et al published surgical rates within 12 months of IBD diagnosis (Vind et al., 2006). They found 12% of the Danish CD patients requiring a surgical procedure within a year of diagnosis. The rate of surgery was lower for
UC (6% at one year). In contrast, a population-based inception cohort study from Olmsted County published in 2001 by Faubion et al revealed much higher surgical rates than this (Faubion et al., 2001). Within 12 months of diagnosis, 38% of CD cases and 29% of UC cases required operation. However, when reviewing this paper it is clear they have selected only those cases in the inception cohort who required steroids early after diagnosis. When re-calculated for the entire inception cohort, the surgical rates for CD were 16% and for UC 10% at 12 months. Longer term follow-up of a large Norwegian population-based inception cohort demonstrated 10 year surgical rates of around 40% for patients with CD (Solberg et al., 2007).

As this study was performed within a ‘real-world’ community environment, it allowed a unique insight into the practicality of managing newly diagnosed IBD patients outside of the hospital-based environment. The research team involved in the pilot registry had a purely observational role. They had no impact on patient care, and thus did not influence timing or choice of therapy. It is, however, possible that the local clinicians may have changed their practice with the knowledge that we were undertaking a study in the area, the Hawthorne effect.

The rate of antibiotic use in this newly diagnosed IBD cohort was low (8%). Only CD patients received antibiotic therapy, with the majority of antibiotic use was to treat perianal sepsis, a recognised indication for the use of antibiotics in IBD (Bernstein et al., 2010a).

The rate of 5-ASA prescription was high in this cohort. In total, 50 patients (70% of the cohort) were commenced on either sulfasalazine or an alternative oral 5-ASA agent within three months from diagnosis. There was a non-significant trend toward increased use of oral 5-ASA agents with more extensive colonic disease location, both for UC and CD. All patients with pancolonic UC received oral 5-ASA therapy. Further sub-phenotype analysis revealed that of all patients commencing oral 5-ASA agent, 6 had IBDU (100% of all IBDU cases), 14 had UC (64% of all UC cases), and 30 had CD (70% of all CD cases), showing higher rates of 5-ASA use in CD rather than UC in this population. This observation is important as there is controversy regarding the efficacy for 5-ASA medications in CD management, with substantial costs involved in the prescription of these medications (Wong and Bressler, 2008, Van Assche et al., 2010). As a comparison, Vind et al also documented high 5-aminosalicylate use in their inception cohort, with 61% of CD patients and 82% of UC patients on 5-ASA medications within 12 months of diagnosis (Vind et al., 2006). Similar high rates of 5-ASA use for UC were seen in the European collaborative EC-IBD cohort, ranging from 62 – 90% within four years of diagnosis (Witte and al, 2000). An Australian survey of Gastroenterologists published in 2007 revealed that 96% of those surveyed used 5-ASA agents routinely in CD patients, although this was not limited to new cases (Gearry, 2007).

Prescription regulations within Australia require clinicians to use sulfasalazine as the first-line 5-ASA, except where an intolerance or allergy to sulphur based medications exist. This will have influenced the prescription patterns observed in the Barwon cohort, with 27 patients first prescribed...
sulfasalazine (54% of all patients receiving an aminosalicylate). A significant observation from this cohort was that one third of patients demonstrated a serious intolerance to sulfasalazine, requiring cessation of therapy. All these cases subsequently commenced an alternative 5-ASA agent, and no subsequent drug reactions recorded. Importantly, of those patients who first initiated 5-ASA treatment with a non-sulfasalazine formulation, none developed drug-related side effects. Therefore, a third of patients who commenced sulfasalazine required a disruption in therapy, hence experienced a delay in receiving appropriate 5-ASA treatment. This may have potential clinical implications, delaying time to remission and negatively influencing health-related quality of life. Long term observation of this group of patients will be important to clarify this further.

A high proportion of IBD patients in this cohort received systemic corticosteroid therapy. Intravenous steroids were administered to 9 patients (13%), while 42 received oral therapy (59%). Factors associated with the need for intravenous steroid use in this cohort were female gender, a diagnosis of UC, extensive colonic disease regardless of IBD type, and a younger age at diagnosis. However, logistic regression analysis revealed that it was only the initial clinician’s assessment of disease severity at diagnosis that predicted the need for intravenous steroids, a result which is likely to reflect the limitations of the small sample size analysed.

A significant proportion of patients remained on oral steroids three months from diagnosis (21% of cohort). A diagnosis of CD was associated with a slightly higher rate of steroid use (63% CD patients, 55% UC patients and 50% IBDU patients, p=N/S). By comparison, in their recent Danish population-based cohort Vind et al found that no patient required intravenous steroid at diagnosis, while their rate of oral steroid use was 51%, similar to that seen in the Barwon group. Slightly older data from the IBSEN cohort from Norway revealed lower rates of 12 months steroid use in newly diagnosed UC patients, with only 24% requiring at least one course of systemic steroids (Moum et al., 1997b). The median age for the EC-IBD UC cohort was 46 years, with 53% having distal disease and 24% with pancolitis. In contrast, the Barwon UC cohort had a median age of 39, with rates for distal disease of 27%, and for pancolitis of 41%. Overall, these differences suggest a more aggressive and extensive disease phenotype in the Barwon cohort, requiring more intense therapy from diagnosis.

Immunosuppressive therapy was commenced in 8 patients (11% of the cohort). All these patients were diagnosed with CD. No IBD patient received a biological agent within three months of diagnosis. The median age of those receiving immunosuppressive therapy was younger than those not receiving an immunosuppressive (19.5 years compared with 39 years, p not significant), suggesting a more severe disease phenotype in the younger age group. Vind et al documented therapy with either Azathioprine, 6-MP or Infliximab in 17% of their inception Danish cohort within 12 months of diagnosis. When they examined medication use for IBD subtypes, the rates were much higher for CD than UC (32% versus 8%) (Vind et al., 2006). Similar low rates in immunosuppressive therapy have also been published from the IBSEN cohort (Moum et al., 1997b). Recent observation of a population-based cohort from Western Hungary suggest higher rates of immunomodulators use
in more recent years, with 12-month rates of Azathioprine use up to 35% (Lakatos and al, 2012). Longer observations of the Barwon cohort will be important to compare these results.

It is important to review the restrictions regarding access to biological agents for IBD in Australia when considering the fact that no IBD patients received this class of medication, despite good evidence for increased healing, reduced hospitalisation and reductions in surgical rates (Van Assche et al., 2010, Lichtenstein et al., 2009). Firstly, they are only subsidised in Australia for CD, not UC. Secondly, there are strict rules relating to when a biological can be introduced. With regard to luminal CD, patients need to have demonstrated a failure to respond to corticosteroids over a 6 week period, in addition to failing an adequate trial of immunosuppressive therapy over at least 3 months. These regulations are therefore likely to have impacted the observed rate of biologic use, despite a significant number being steroid dependent by three months. Newer guidelines introduced after the cohort data was collected now allows earlier access to these agents in the setting of perianal disease. This should be reflected in the 12 month outcome and treatment data for this new cohort when it is collected.

6.8 CONCLUSION/FUTURE DIRECTIONS

Clinical registries provide reliable and clinically useful information regarding disease rates, disease behaviour and patient outcomes. They have previously been successful in monitoring healthcare performance and treatment efficacy in many real-world environments. This section of research has shown that, with appropriate planning, it is possible to establish a high quality population-wide IBD registry, incorporating newly diagnosed patients prospectively. The short-term three month outcome assessment further demonstrates the clinical utility of the registry, providing important and novel real-world data regarding very early disease course in a regional Australian setting.

This pilot study has provided a strong foundation for future research. The community-based IBD inception cohort that forms this pilot registry will now be prospectively observed to allow unique short, medium and long-term disease evolution observations. By clearly defining these cases at the time of disease onset and subsequently observing those who develop a complicated course, it is hoped that features predicting a more severe disease course may become apparent. This would allow clinicians to accurately identify patients at the highest risk of progression and disease-related disability, and to then target more aggressive therapies for these individuals at an early stage. For example, the early use of aggressive immune suppression or biological agents may be appropriate for these patients, aiming to reduce disease-related complications. In addition, extensive lifestyle and background data will be assessed, allowing an exploration of possible aetiological associations. Finally, the local cohort will be compared to newly diagnosed IBD cases in other regions. This will include collaboration within the Asia-Pacific region, and direct comparisons with newly established population-based inception cohorts in Europe.
CHAPTER 7. THESIS SUMMARY

This thesis presents the key results of a prospective, observational population-based research project assessing local IBD epidemiology, providing regional IBD incidence and prevalence rates. This research has allowed valid Australia-wide IBD rate estimates through the extrapolation of local results. The research has also demonstrated that it is feasible to establish a community-based IBD registry by collecting robust disease-specific and demographic data on all newly diagnosed cases. This thesis has demonstrated that by adhering to established population-based epidemiological methods, high quality and reliable information regarding disease incidence, prevalence and disease behaviour can be produced. The results of this research thus make an important contribution to the current local and global knowledge regarding the evolution of IBD epidemiology.

LOCAL IBD INCIDENCE RATES, RECENT RATE CHANGES, DISEASE PHENOTYPES AND CLINICAL DETAILS OF NEW IBD CASES IN BARWON.

An extensive population-based assessment of local IBD incidence was successfully made. The study population was the Barwon region, a geographically and demographically defined regional Australian population. This study utilised capture-recapture methodology integral to maintaining high case ascertainment rates and maximising the validity of the final disease rate estimation. Strict internationally recognised diagnostic criteria, with clinically-focused case confirmation, further increased the strength of the current study findings.

This project confirmed that the local Barwon region maintains a high rate of newly diagnosed IBD cases when compared to other recent global population-based estimates (Jacobsen et al., 2006, Geary et al., 2006, Bernstein et al., 2006, Rubin et al., 2000). In addition, Crohn’s disease is the most common sub-type of IBD.

Furthermore, the current results suggest that the local IBD incidence rate has remained stable over the last 3-4 years, with no statistical difference between the current results and historical rates in this population calculated previously by Wilson et al (Wilson et al., 2010). This result supports recent publications suggesting that in Western populations there has been a relative stabilization of IBD rates, despite the increase in disease frequency that had been observed over the preceding 50 years (Baumgart et al., 2011).
Although the crude number of cases in the current study is comparatively small and limit the significance of some findings, subtle changes in local IBD phenotype have been demonstrated. The more recent IBD cohort trended towards a higher percentage of cases with more colonic disease, true for both CD and UC. For example, the present UC cohort had a higher percentage of pancolitis compared to the 2008 cohort (41% versus 17%, p = 0.058). Moreover, a significantly higher proportion of CD cases in the current cohort had ileocolonic disease (44% versus 24%, p = 0.042). It is difficult to determine whether these subtle disease location findings reflect a local change in disease pathogenesis, or relate to the small absolute case numbers in the two cohorts.

Due to the clinical focus of data collection, significant amounts of data relating to investigations, symptoms and demographic information were collected and analysed. Whilst all new cases underwent colonoscopy and biopsy during symptom assessment, a significant proportion also underwent a range of additional tests including imaging procedures, additional pathology testing, and further endoscopy. For example, 7% of the cohort underwent capsule endoscopy, the role of which in IBD diagnosis is beginning to emerge (Ali and Tamboli, 2008, Maunoury et al., 2007). While a wide spectrum of symptoms were present in this cohort, a number of trends were evident, some reaching statistical significance. For example, while diarrhoea was the most common presenting complaint in both CD and UC patients, abdominal pain was far more common in CD, while PR bleeding and mucous was seen more frequently in UC.

Given the demographic similarities between the study population and the broader Australian community, the local incidence results provide the opportunity to revise national IBD incidence data. During the period of 2010-2011 it was estimated that over 5400 cases would have been diagnosed across Australia, with CD being most common. This is significantly greater than previous estimates.

**LOCAL IBD PREVALENCE RATES, DISEASE PHENOTYPES AND BURDEN OF CARE PROVIDED IN GENERAL PRACTICE.**

This research has provided Australia’s first prospective IBD prevalence rate data. While based on the methodology used in the incidence rate study, the prevalence study required significant expansion into the primary care environment. The results have provided novel insights into the true local disease burden related to IBD, and also the workload that General Practitioners in Australia face with regard to IBD management and follow-up.

IBD prevalence rates in the Barwon region are high (344.6/100,000 95% CI 309.6-383.4/100,000), and are comparable with some of the highest estimates from previously studied western cohorts (Jacobsen et al., 2006, Bernstein et al., 2006, Gearry et al., 2006, Loftus et al., 2007). As with the results of the incidence study, CD is the more common form of IBD in the local region. The highest
prevalence rates for CD were observed in the 25-54 year age group, while for UC the prevalence rates continued to increase with age. One explanation for this pattern may reflect on a more recent increase in CD rates when compared to UC. Although direct comparison is limited by differences in study methods, the prevalence of IBD in Australia would appear to have risen dramatically over the last 15 years when comparing the current results to those obtained by Anseline et al (Anseline, 1995).

Because of demographic similarities between the local study population of Barwon and the wider Victorian and Australian populations, the local results have also provided the opportunity to update national IBD prevalence estimates. This has confirmed the high burden of disease in the Australian population, with revised prevalence rates considerably higher than previously published estimates from 2006. Although extensive health-care cost modelling was not undertaken as part of this thesis, revised health-care related expenditure estimates for IBD in 2011/12 based on previously published estimates exceeds 3 billion Australian dollars.

Important data on paediatric IBD rates have also been produced as part of this comprehensive prevalence study. The current paediatric IBD prevalent cohort is the largest yet to be reported in Australia. Similar to the adult findings, paediatric IBD rates are also comparably high when compared to international cohorts, with crude rates of 46.4 and 19.9 per 100,000 for CD and UC respectively.

Almost a third of prevalent case details came from General Practice sources alone. This represents a significant number of IBD patients who are not being seen in specialist care settings in a 12 month period. Although many of these patients would be predicted to be in clinical remission, a number of important management issues still should be addressed in these patients, including compliance, assessment of disease activity, vaccination issues, cancer risk, osteoporosis assessment, nutritional and psychological problems, the early recognition and management of IBD relapses and cancer surveillance as necessary. These results highlight the importance of providing continued education for GP’s regarding the optimum management of IBD patients.

LONGITUDINAL OBSERVATION OF A NEWLY ESTABLISHED IBD INCEPTION COHORT; THREE MONTH OUTCOME DATA OF THE PILOT BARWON IBD REGISTRY.

The utility, feasibility and practicality of establishing a population-based IBD registry was assessed during the final stage of this research project. Using the opt-out consent process, the current pilot IBD registry was successful in recruiting all incident cases. This shows that by adhering to strict epidemiological principles, a high quality cohort of patients can be established, maintaining useful
and reproducible details. In addition, longitudinal observation of this novel community-based IBD
inception cohort has provided a unique insight into the very early progress of newly diagnosed IBD in
Australia, away from tertiary referral centres.

Three month follow-up data revealed relatively high rates of hospitalisation, steroid use, and
surgery, particularly for CD patients, when compared to cohorts described elsewhere (Bernstein and
Nabalamba, 2006). Perianal disease was a strong predictor for the need for surgical intervention. 5-
ASA use was high in this inception cohort, irrespective of a final diagnosis of CD or UC. A trend
toward oral therapy being used more frequently in more extensive disease was observed, however
small study numbers limited the significance of this result. Significant rates of sulfasalazine
intolerance were documented, often leading to a delay in institution of potentially efficacious oral 5-
ASA therapy.

CONCLUSION.

This research has been successful in its primary aims. It has provided updated population-level IBD
incidence rate data, produced novel Australian IBD prevalence rate data, and led to the successful
establishment of a unique population-based inception cohort through an IBD registry. While this
registry has already provided the opportunity to observe very early clinical features of newly
diagnosed IBD cases, further observation of this cohort over the coming years will provide invaluable
local data on IBD behaviour in a contemporary Australian population-based setting.

DIRECTIONS FOR FUTURE EPIDEMIOLOGY RESEARCH.

The study of IBD epidemiology remains an important focus of research. It will further allow the
recognition of certain phenotypes and the impact this has on disease evolution. In addition, an
improved understanding of IBD pathophysiology and recognition of risk factors for disease onset and
progression will be possible. Wherever the research is undertaken, it will be crucial to not only
define disease incidence and prevalence rates, but also to incorporate longitudinal studies of these
cohorts linking assessment of biochemical, microbiological and genetic factors to disease onset and
outcome. The most useful information will be gained from well-designed, methodologically sound
population based studies that confidently and systematically identify patients with IBD at the start of
their disease course, and focus closely on the early phase of the disease evolution.

Future epidemiology study in IBD must remain primarily population based. In contrast to studies
performed on patients seen in hospital referral centres, population based epidemiology research
provides a more complete and less biased view on the true spectrum of IBD. The use of validated
disease diagnostic criteria, and prospective case ascertainment will be crucial to the validity of future
studies. In addition, the length of observation needs to be extended to allow for a better
understanding of the possible impact of therapies on disease related outcomes. By adhering to more
rigorous study designs around the world, and standardising the minimum requirements for high quality epidemiology study, future comparisons of results between different centres will be more meaningful. Cooperation and collaboration between researchers from different areas of the globe will then be more reliably possible, greatly increasing the power of the research undertaken.

The Barwon incident cohort will continue to be observed for disease behaviour and impact into the future. To increase the cohort size, ongoing recruitment of incident cases will be facilitated. Furthermore, future population-based projects are planned in new geographic locations in Australia. A large scale IBD epidemiology project will commence in 2013, incorporating the entire southern state of Tasmania. This will assess IBD incidence, prevalence and disease evolution in a geographically isolated population of over 500,000 people, and will act as a direct comparison population to the existing Barwon cohort.
Appendix 1.

Incident IBD case data collection proforma.

**IBD Incident Case Proforma**

Case number -

**Demographics**

Name -
DOB -
UMRN -
Medicare number -
Phone -
Address -

**Disease Specifics**

Date of Diagnosis -
Referral source -
Main symptoms -

Length of symptoms prior to diagnosis -

Scope date and results -

Histology -

**Disease Progress during study period**

1) Medications used (with dates);
   - Antibiotics -
   - Steroids (IV/oral/topical) -
   - 5 ASA (oral/topical) -
   - Immunosuppressants -
   - Biological agents -

2) Admissions related to disease

3) Surgical procedures

**Imaging** -

Microbiological samples –
Appendix 2.

IBD case confirmation three months from initial notification data collection proforma.

Three months from diagnosis – Review.

Name -
DOB -
Study Case Number -
Date of first diagnosis -
Date of review –

1. Surgery
   Any surgery < 3 months
   If Y then operation details and dates;

2. Hospital admissions
   Any admissions related to IBD < 3 months
   If Y then details and dates;

3. Medications used < 3 months (include dates, doses)
   Abx
   Steroid
   5-ASA agents
   IM’s
   Biologicals
   Other

4. Montreal classification at 3 months from dx
   (CD A1-3 L1-4 B1-3 p / UC E1-3)
Appendix 3.

Prevalent IBD case notification data collection proforma used by local paediatricians.

**IBD prevalence study Geelong Region July 2010-June 2011**

Prevalent Inflammatory Bowel Disease (IBD) cases

**Paediatrician Identified Patients**

1) patient initials  
2) date of birth or age  
3) gender  
4) type of IBD (Crohn’s Disease, Ulcerative colitis, Proctitis, etc)  
5) year of diagnosis (if known)  
6) current postcode or suburb (to confirm residence in catchment area)  
7) date last seen through the practice (to confirm still living in the area)

Thanks very much for your assistance in this research, we really appreciate the time and effort in providing this information.

Dr Corrie Studd

IBD Fellow

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Mobile 0420 975 715
Pilot Inflammatory Bowel Disease Registry

Dear;

You have received this letter as we believe you may have been recently diagnosed with one of the Inflammatory Bowel Diseases (IBD), either Crohn’s Disease (CD), Ulcerative Colitis (UC), or IBD-unspecified (IBDU).

Previously, there has not been a structured or consistent way of following the progress of patients who have been diagnosed with Inflammatory Bowel Disease (IBD). We wish to establish the regions first IBD registry. A registry is simply a secure database containing some of your health information.
To maintain the most complete information, you may be contacted by a member of our research team at some stage in the future, either by telephone, email or standard mail. At that point you will be under no obligation to answer any questions or take part in any future research in IBD. If you are happy to be involved, your details will remain strictly confidential, and will never be released to a third party. Also, if any important results relating to this research are published in the future, no individual identifying data will be released, so that your confidentiality is always maintained.

To keep your details in this pilot registry you don’t have to do anything. In our registry, as in other large Australian registries for different diseases like diabetes or heart disease, we use an “opt-out” consent process. You don’t need to fill out any forms or paperwork as your details are automatically recorded. However, remaining in this registry is entirely voluntary. You are free to withdraw your consent for involvement in the registry at any stage, and this decision will have absolutely no influence on your medical care in any way. You can withdraw your consent easily by contacting our research team directly, using the contact details provided on the bottom of this form.

Also, please feel free to contact myself if you have any other questions involving the pilot registry or this research project. This pilot registry has been approved by the Barwon Health Medical Research Ethics Committee.

Thanks for your help in this very important work.

Dr Corrie Studd.

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