The Epidemiology, Phenotype and Disease Course of Australian Children with Inflammatory Bowel Disease.

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Abbreviations

ACT	Australian Capital Territory
ANOVA	Analysis of variance
APAIBD	Australian Paediatric and Adolescent Inflammatory Bowel Disease database
ASCA	Anti-*Saccharomyces cerevisisae*
ASA	Aminosalicylates
BMI	Body mass index
CARD15	Caspase recruitment domain-containing protein 15
CD	Crohn's disease
CI	Confidence interval
CRP	C-reactive protein
EIM	Extra-intestinal manifestation
ESR	Erythrocyte sedimentation rate
GIT	Gastrointestinal tract
Hb	Haemoglobin
HR	Hazards ratio
Ht	Height
IBD	Inflammatory bowel disease
IBD1	Inflammatory bowel disease protein 1
IBDU	Inflammatory bowel disease unclassified
IC	Indeterminate colitis
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IQR	Interquartile range
N	Number of children
NOD2	Nucleotide-binding oligomerization domain-containing protein 2
NSW	New South Wales
NT	Northern Territory
OFD	Orofacial Crohn's disease
OR	Odds ratio
p-ANCA	Perinuclear anti-nuclear cytoplasmic antibody
PCDAI	Paediatric Crohn's disease activity index
Plts	Platelets
PSC	Primary Sclerosing Cholangitis

PUCAI	Paediatric ulcerative colitis activity index
QLD	Queensland
SA	South Australia
SMR	Standardised mortality ratio
TAS	Tasmania
UC	Ulcerative colitis
UK	United Kingdom
USA	United States of America
VIC	Victoria
WA	Western Australia
WCC	White cell count
Wks	Weeks
Wt	Weight
Yrs	Years

Abstract

Inflammatory bowel disease (IBD) is the term for a group of disorders of the gastrointestinal tract, encompassing Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU). The aims of this study were to review the disease phenotype at diagnosis in children with IBD, investigate any significant associations, determine the incidence in South Australia and to assess the disease course.

Methodology: Phenotypic features at diagnosis of children collected into the Australian Paediatric and Adolescent IBD database (APAIBD) and follow-up details of South Australian children were analysed. Incidence of IBD in South Australia was calculated. Statistical testing included the independent t-tests/ANOVA (parametric), Mann-Whitney/Kruskal-Wallis testing (non-parametric), chi-square analysis, linear and logistic regression, Kaplan-Meier survival, Cox Proportional Hazards, negative binomial regression and linear mixed effects model. $P<0.05$ was considered to be statistically significant.

Results: There were 2101 children diagnosed with IBD during the period 1996-June, 2010. The majority had CD (1247; 59.4%), followed by UC (631; 30%) and IBDU (223; 10.6%). Overall, there was a male predominance (56.4%), which was significantly greater in CD compared to the background Australian paediatric population (58.6% vs 51.3%; $p<0.05$). The majority of children with CD presented with ileocolonic disease (57%; 662), upper gastrointestinal inflammation (78.9%; 816) and inflammatory behaviour (92.6%; 1123). Orofacial CD was present at diagnosis in 8.9% (107/1207) and perianal lesions in 46% (545/1184) of children. There was a significant association between orofacial CD and anal tags ($p<0.0001$), anal fissures ($p<0.0001$), oesophageal inflammation ($p=0.0001$), ocular ($p=0.0016$) and dermatological manifestations ($p=0.001$). Most children with UC presented with extensive colitis (69.6%; 421/605). Children with CD presented with a lower weight, height and BMI z-scores compared to UC. The incidence of IBD, CD and UC in South Australian children aged less than 16 years was 6.43, 3.62 and 2.31 per 100,000 person years respectively during 1996-2009.

The majority of children were treated with systemic corticosteroids (85% CD; 70% UC) with a clinical remission rate of at least 70% at 6 weeks. Half of these children had a subsequent clinical flare-up within the first year. Compared to CD, a greater proportion of children with UC developed mucosal healing within 5 years ($p=0.0037$). The risk of developing intestinal strictures or fistulae was 15% at 5 years in CD. Mean duration of systemic corticosteroid use

was 69.3 and 59.7 days per year for CD and UC, respectively. The mean duration of hospitalisation was 5.29 days per year for CD and 6.07 days per year for UC. The rates of intra-abdominal surgery were 16% in CD and 13% in UC within the first 5 years. Weight and BMI parameters improved within the first year following diagnosis in both CD and UC, although the low height z-scores in CD did not improve, despite medical therapy. Two children with CD died as a result of sepsis.

Conclusion: Paediatric IBD is a heterogeneous disease, which impacts upon a child's health. Despite attaining remission, children are at risk of clinical recurrence, changes in extent and behaviour, side-effects from systemic corticosteroids, surgery and poor growth. Thus, there is a need for improved management to avoid these complications.

Declaration Statement

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Dr Rammy Abu-Assi,
1st of April, 2014.

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Chapter 1: Introduction

Inflammatory bowel disease (IBD) is a heterogeneous condition, with complexity in aetiology, anatomical involvement and clinical presentation. It encompasses the disease subtypes of Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis/inflammatory bowel disease unclassified (IC/IBDU). Differentiation is dependent upon the distribution of the disease, endoscopic findings, presence of granulomata and impact upon growth.

Ulcerative colitis was the first condition to be clearly differentiated among many reports of patients who suffered from prolonged diarrhoea. Descriptions of chronic non-infectious bloody diarrhoea, in keeping with ulcerative colitis date back to Hippocrates and the Romans.[1, 2] Several labels have been used in the literature. Sir Samuel Wilks was the first physician to use the term "ulcerative colitis" in a case report in 1895.[1, 2] Thereafter, this term began to be used more frequently within the medical literature.

Likewise, Crohn's disease or terminal ileitis as it was traditionally named may have been described as far back as Hippocrates.[1, 2] Morgagni[1] described a young man with ileal ulceration and enlarged regional lymph nodes who died from perforation in 1761. Following this, many reports were published describing disease involving the ileum and caecum with the presence of granulomata and mesenteric lymphadenopathy. It was not until 1932 that, a landmark paper was published in the Journal of the American Medical Association (JAMA) by Crohn, Ginzbury and Oppenheimer with a contribution from Dr Berg describing 14 cases of terminal ileitis.[3] Following this, the term "Crohn's disease" was introduced for this distinctive type of chronic gut inflammation, differentiating it from ulcerative colitis.

Both ulcerative colitis and Crohn's disease are considered part of a spectrum of chronic gastrointestinal inflammation. The underlying aetiology and pathophysiology are multifactorial and complex. It is thought that the inflammation within the gastrointestinal tract occurs as a result of a dysregulated immune reaction in response to an environmental factor and/or bacterial content within the intestinal lumen, in the presence of abnormalities of the mucosal lining in a genetically predisposed individual. Much research has been conducted, and continues to be undertaken, to gain a better understanding of this inflammation, hopefully allowing targeted therapy.

Ulcerative colitis is a continuous mucosal disease of the colon, extending proximally from the rectum. On the other hand, Crohn's disease is a transmural inflammatory process, with a predisposition to granulomatous inflammation, involving any part of the gastrointestinal tract, but predominantly the terminal ileum and/or colon. The differentiation between the two subtypes, and a description of the confusion generated in studies in which a clear distinction is difficult, will be discussed in this thesis.

Inflammatory bowel disease may affect both adults and children. Many studies have reported on its epidemiology, which has changed over time. This will be discussed in the upcoming chapters. There are more epidemiological studies in adults, but the study of children provides a unique opportunity to describe this disease as it evolves, coincident with the maturation of the immune system. It has been shown that the diagnostic phenotype changes from early childhood to adolescence and then adulthood. The current gap in the literature, relates to descriptions of children with orofacial and/or perianal Crohn's disease, potentially reflecting a distinct disease process. Furthermore, there is an inadequacy in the understanding of the extra-intestinal manifestations and the impact upon nutrition and growth.

The natural history of inflammatory bowel disease is just as important. Several studies have described disease course in terms of a single parameter, which may be poorly defined. It may have significant impact upon various facets of a child's health, growth and psychosocial wellbeing. Within this thesis, the disease course according to several clinical markers will be studied and the appropriateness of individual parameters will be further discussed.

The aim of this project is to review the literature on the epidemiology, disease phenotype and natural history of inflammatory bowel disease in children. Gaps in knowledge will be highlighted. The diagnostic phenotype of Australian children will be described and comparison with international cohorts, given the regional variation, will be undertaken. Then, the disease course of South Australian children following diagnosis till transition to adulthood will be described.

Chapter 2: Epidemiology of Paediatric Onset Inflammatory Bowel Disease

2.1: Introduction

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems".[4] It is the study of disease occurrence with regard to both new (incident) and existing cases (prevalent).[5] Details about incidence, prevalence, temporal trends and relationship to demographic features, such as age, gender, family structure, location of residence and other factors are referred to as descriptive epidemiology.[5] Epidemiological studies are important in delineating the disease burden and providing clues to possible factors that may be influencing the onset and natural history of the disease.

Inflammatory bowel disease (IBD) is a chronic relapsing disease of world-wide distribution affecting all age groups. The approach to assessing the epidemiology of IBD tracks the incidence in defined populations and, documents and follows the impact of the disease on patients, their family and the wider society.

IBD is a heterogeneous condition with multiple factors contributing to the onset of inflammation. The exact trigger for inflammation is unknown, but is the focus of ongoing research. In simplistic terms, it is the result of a dysregulated immune response in a genetically predisposed individual to an environmental trigger in the setting of defects in the mucosal lining and altered gut flora.

IBD can occur at any age but it is generally considered that up to 25% of incident cases occur in those under 20 years of age.[6] The paediatric population is considered ideal for further epidemiological research because children may not have been exposed to as many environmental factors and those exposures that have occurred may be limited in both number and duration. Comparisons between the epidemiology of disease in both paediatric and adult populations may help define differences in the genetic, immunological and environmental milieu.

Epidemiological studies of paediatric inflammatory bowel disease are fewer in number than adult studies, and most have been conducted in Northern Europe, Canada and the United States of America. In the following chapter, a review of the descriptive epidemiology of

paediatric onset disease is presented and pertinent adult studies also examined. However methodological differences and case definitions vary between studies, influencing the comparability of the data, therefore these methodological issues are considered first.

2.2: Limitations in comparing epidemiological studies

2.2.1: Defined upper age limit of the paediatric cohort

An important discrepancy among studies is the defined upper age limit for the paediatric population which may range from 15 to 19 years of age.[7-9] Considering that the peak incidence begins during adolescence and continues till the third decade of life, variation in the upper age limit that defines paediatric and adult onset disease will impact the overall incidence figures and make comparison difficult.[6] Thus, studies with a higher defined age limit reported a higher incidence figure.[10, 11]

2.2.2: Diagnostic Criteria for IBD and Disease Subtype

IBD includes two principle disorders that have distinctive features, namely Crohn's disease (CD) and ulcerative colitis (UC), however there can be significant overlap clinically, histologically and endoscopically between the two and hence considerable effort has been made to establish a diagnostic criteria. The classification into CD, UC and inflammatory bowel disease unclassified (IBDU) is not always straight forward, causing misclassification and exclusion of some children. Classifying IBD into CD, UC or IBDU is based on a range of clinical, radiological, serological, endoscopic and histological features, in addition to the clinician or researcher's experience in differentiating disease subtypes. Early studies used the Lennard-Jones criteria, which introduced the sub-classification of "probable" and "definite" (table 2.1).[12] There was variation among studies whereby children with "probable" CD or UC have been excluded from the study cohort, under-estimating incidence figures and excluding an important cohort of children.[13-15]

Table 2.1: Lennard-Jones criteria for the diagnosis of CD and UC.[12]

	Crohn's disease (CD)	Ulcerative colitis (UC)
Inclusion criteria	Granulomatous inflammation anywhere from mouth to anus. Discontinuous inflammation/lesions. Transmural inflammation. Fibrotic inflammation (strictures). Lymphoid aggregates on histology. Retention of colonic mucin on biopsy. Presence of granulomata.	Continuous mucosal inflammation extending from the rectum proximally along the colon.
Exclusion criteria	Infections. Ischaemia. Irradiation. Lymphoma/carcinoma.	Infections. Ischaemia. Irradiation. Solitary ulcer. Small bowel inflammation. Complex anal lesion. Granuloma in any biopsy.
Subclassification	Probable or definite CD. Indeterminate colitis.	Probable or definite UC. Indeterminate colitis.

In order to provide a uniform diagnostic approach to IBD and sub-classification into CD, UC and IBDU, the Porto criteria was established by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in July 2005 and then further clarification of atypical findings in a North American clinical report.[16, 17] In the Porto criteria, any child with chronic symptoms (abdominal pain, diarrhoea, rectal bleeding and weight loss) of at least four weeks duration, or recurrent episodes of at least twice within six months, physical findings indicative of gut inflammation and/or extra-intestinal manifestation, and laboratory parameters suggestive of IBD (anaemia, thrombocytosis, hypoalbuminaemia, raised erythrocyte sedimentation rate and/or c-reactive protein, positive anti-Saccharomyces cerevisiae antibody or perinuclear anti-neutrophil cytoplasmic antibody) with the exclusion of gastrointestinal infections should be investigated further for IBD by endoscopy and colonoscopy with ileal intubation.[16] Endoscopic and histological distinction between CD and UC in the Porto criteria is presented in table 2.2. Oral CD includes lip swelling, gingival hyperplasia and aphthous ulcers, and perianal disease includes tags, fissures, fistula and abscess.[16] The Porto criteria recommend further investigation for small bowel disease if a diagnosis of CD is established or that of UC is uncertain. IBDU is defined as acute and chronic inflammation confined to the colon, no evidence of lymphocytic or allergic colitis, lack of small bowel disease assessed radiologically, and no definite histology in keeping with CD or UC.[16]

In the clinical report from the Working Group of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, and the Crohn's and Colitis Foundation of America, further distinction among the disease subtypes with discussion of atypical findings and a more stringent algorithm to sub-classification was recommended.[17] The major conclusion from the report was that the presence of gastritis, ileitis with pancolitis, periappendiceal inflammation with left sided colitis and/or relative rectal sparing should not exclude the diagnosis of UC.[17] The majority of recent paediatric studies have utilised the Porto criteria.[16]

The definition of IC/IBDU has not been consistent. The original definition of IC was a pathological one, based on colectomy samples for severe disease (fulminant colitis) in which the inflammation was not conclusive for either UC or CD. Subsequently it was used to describe children with atypical colitis that did not fulfil the criteria for either CD or UC. Such children were excluded from the various studies, under-estimating the true incidence figure and limiting research into this distinctive cohort that may evolve into either CD or UC. Thus, the definition of IC has been modified in the recent Montreal Classification to encompass only patients who have had a colectomy and IBDU for those who have not had a surgical resection, when a clear differentiation into CD or UC could not be established.[18]

Table 2.2: Endoscopic and histological differentiation between CD and UC according to Porto criteria.[16]

	CD	UC
Endoscopic (including visualisation of oral and perianal area)	Ulcers (aphthous, linear or stellate). Cobblestoning. Patchy distribution with skip lesions (no inflammation). Fistula. Abnormalities in oral and/or perianal.	Ulcers. Erythema. Loss of vascular pattern. Granularity of the mucosa. Friability. Pseudopolyps. Continuous inflammation from the rectum to the proximal colon.
Histology	Acute and chronic inflammation with architectural changes, loss of glands and branching of crypts. Inflammation beyond the mucosa (submucosal/transmural). Ulcers. Crypt distortion and/or abscess. Non-caseating granulomata. Focal changes. Patchy distribution.	Acute and chronic inflammation with architectural changes, loss of glands and branching of crypts. Mucosal involvement. Crypt distortion and/or abscesses. Goblet cell depletion.

Despite the above guidelines on diagnosis and differentiation among the disease subtype, most reported cases are done by the treating physician who may ultimately make the classification based upon their own experience. In addition, some clinicians may opt not to report difficult to differentiate cases such that their diagnostic decision would not be criticised. Conflicts in disease subtype may be avoided by following the above criteria and clinical report, and having all reported cases in a multicentre study reviewed by a central facility blinded to the initial classification. Undertaking such a review would be costly and time consuming, but would have the benefit of providing uniformity.

2.2.3: Population Size

Paediatric epidemiological studies suffer from smaller sample size because of lower disease incidence and prevalence compared to adult studies.[7, 8, 19, 20] Some studies were single centred where study numbers were further reduced, between 44 and 152 children, negatively impacting upon the opportunity of finding associations of potential significance.[6, 8, 21-25] Multi-centred studies in such a chronic illness of low incidence has the obvious advantage of capturing greater numbers and improving the power of statistical analysis and allowing much greater value from subgroup analysis.

2.2.4: Retrospective versus Prospective Studies

There are limitations in retrospective studies with regard to identification of cases, non-uniformity of investigations and errors in diagnostic classification. By their nature, retrospective studies rely on recorded information and have the potential for missing information. Data needs to be attained from the patient's record or by means of the patient or carer's recollection, potentially allowing inaccurate recall and bias. Lack of complete data and the inability to attain further pertinent information may lead to uncertainty in the diagnosis and classification, prompting the researcher to exclude such children from further analysis, contributing to an under-reporting of the incidence. In addition, any misclassification of disease subtype may be difficult to review as the original history, examination and investigations may not be easily accessed or interpreted. Prospective studies on the other hand are more likely to capture incident cases, allowing uniformity in history, examination and investigations, leading to accurate data acquisition and better disease classification.

2.2.5: Case Ascertainment

There are differences among the studies with regard to the methodology of case ascertainment. New paediatric IBD cases may be identified by hospital discharge databases, physician reporting or pathology records of gastrointestinal biopsies. Hospital discharge databases may be limited by the fact that some children may be assigned either a diagnosis that is incorrect or incomplete. Therefore, such cases if identified will need to be reviewed by means of discussion with the treating clinician, examination of written and electronic notes, and review of all investigations. Furthermore, hospital based data collection are limited to those sicker children who required inpatient care, excluding those diagnosed in the community with mild disease. Thus, the true incidence within a population may be under-estimated.

Population based studies with physician notification to a central database may capture a wider population with variable severity, but limited by the time constraints and perceived inconvenience of reporting data in addition to a busy clinical load. Some physicians may be reluctant to report difficult diagnostic cases or those with poor outcome, thereby avoiding potential criticism. An improved means of data capture may include the utilisation of a regional or national health administrative database in which the diagnosis of all community and hospital consultation and procedures are recorded.[19, 26, 27] Accuracy of the diagnosis will need to be verified by review of the clinical records.

Pathology based case ascertainment is better but relies on all pathology centres being involved in the study, and there needs to be a system of reviewing histological specimens with the clinical details so that the diagnosis of IBD is confirmed. Reviewing the clinical information with different physicians, clinics, laboratory services and hospitals is a daunting task.

These differences are highlighted in the study by van der Zaag-Loonen et al[28] on the incidence of paediatric IBD in the Netherlands between 1999 and 2001. They utilised both a physician based reporting registry by paediatricians and a national pathology database, in which a total of 546 children, aged less than 18 years of age were identified with IBD. The physician reporting was based on agreed Dutch guidelines on the diagnosis of IBD according to clinical, radiological and histological findings. Within this cohort, 32 children (6%) were identified by physician reporting only, 188 (34%) by both physician reporting and the pathology database,

and 326 children (60%) were identified only from the pathology database. Relying only on physician reporting ascertainment would have missed 60% of new IBD cases. In contrast, the pathology ascertainment method over identified cases with 729 children with histology suspicious of IBD, of which 514 (71%) were confirmed as IBD following review of the clinical information.

Another flaw of physician reporting within this Dutch study was that a peak IBD incidence was demonstrated at 14 years of age because some older adolescents were missed as they were treated by adult gastroenterologist and surgeons, not by paediatricians. This is not reflective of the true rise in incidence throughout adolescence into young adulthood. In contrast, the pathology based reporting showed this continued high incidence of IBD into early adulthood.[28] Therefore, the upper age limit for children may need to be restricted to those aged less than 15 years in paediatric studies.

The diagnosis of IBD relies on clinical symptoms, laboratory abnormalities, and radiological findings with endoscopic and histological inflammation. Thus, no single means of data collection will suffice in identifying all cases.

2.2.6: Derivation of Incidence Figures

Case ascertainment methodology may have a significant impact on incidence data. There are differences among studies in their calculation of incidence figures impacting upon interpretation and comparison of the results. Population data may be presented as crude figures, limiting comparison between temporal periods and regions, given the potential differences in age, gender and ethnicity of children. Adjusting for these will allow comparison of incidence and prevalence figures, improving evaluation of the impact of environmental factors.

2.3: Incidence of IBD

There is variation in the reported incidence of IBD, probably related to the differing means of case ascertainment, defined age limit for the paediatric cohort, temporal and regional differences. The paediatric incidence of IBD, CD and UC are presented in table 2.3.

Table 2.3: International studies of the incidence (per 100,000/year) of IBD in children (≤18 years).

Country	Year	Age	IBD	CD	UC	IBDU
EUROPE						
Britain and Ireland[29]	1998-1999	<16yrs	5.2	3.1	1.4	0.6
Primorsko-Goranska County, **Croatia**[26, 30]	2000-2004	<15yrs		8.69	0.86	
Moravia, **Czech Republic**[23]	1998-2001	<16yrs	2.24	2.69	1.84	0.33
Czech Republic[9]	2001	<15yrs		1.26		
Copenhagen county, **Denmark**[8]	1962-1987	<15yrs		0.2	2.0	
Tampere and Helsinki district, **Finland**[31]	2003	<18yrs	7.0	2.6	3.2	1.0
Finland[32]	2003	<18yrs	15	5	9.1	
Northern **France**[13]	1997-1999	<17yrs	3.1	2.6	0.8	0.12
Ireland[33]	2000-2010	<16yrs	3.9	2.3	1.1	
Italy[34]	2003	<18yrs	1.39			
Netherlands[28]	1999-2001	<18yrs	5.2			
Western **Norway**[35]	1984-1985	<16yrs		2.5	4.3	0.0
Southeastern **Norway**[36]	1990-1993	<16yrs	4.7	2.7	2.0	
Southeastern **Norway**[37]	1990-1994	<16yrs	4.15	2	2.14	
Southeastern **Norway**[38]	1999-2004	<16yrs	5.65	3.64	2.05	
Poland[10]	2002-2004	<18yrs	2.7	0.6	1.3	0.8
Scotland[39]	1991-1995	<17yrs		3.0	1.8	
Scotland[40]	2003-2008	<16yrs	7.82	4.75	2.06	1.01
Oviedo, Northern **Spain**[26, 41]	2000-2002	<15yrs		5.76	1.63	
Spain[42]	2003-2009	<18yrs	2.5	1.7	0.88	
Southwestern **Sweden**[15]	1983-1987	<16yrs	5.3	2.7	1.9	0.7
Sweden[14]	1993-1995	<16yrs	7.0	1.3	3.2	
Northern Stockholm, **Sweden**[22]	1999-2001	<16yrs	10.5	8.4	1.8	0.2
South Glamorgan, **Wales**[43]	1989-1993	<16yrs		3.11	0.7	
Cardiff/the Vale, South **Wales**[44]	1983-1993	<16yrs	5.4	3.6	1.5	
Wales[45]	1995-1997	<16yrs	2.6	1.36	0.75	0.48
NORTH AMERICA						
Metropolitan Toronto, **Canada**[6]	1991-1996	<18yrs		3.7	2.7	
Ontario, **Canada**[27]	2005	<18yrs	11.4	6	4.2	
Wisconsin, **USA**[25]	2000-2001	<18yrs	7.05	4.56	2.14	0.3
ASIA						
Kuwait[46]	1998-2008	<16yrs	2.16	1.53	0.6	0.03
Riyadh, **Saudia Arabia**[47]	1993-2002	<18yrs	0.5			
AFRICA						
Benghazi, **Libya**[48]	2006	<15yrs	0.91			
AUSTRALASIA						
Victoria, **Australia**[21]	1996-2001	<17yrs		2.0		
Victoria, **Australia**[49]	2009	<17yrs		1.61		
New Zealand[50]	2002-2003	<15yrs	2.9	1.9	0.5	

2.3.1: Geographical Differences in Incidence

The majority of paediatric studies with calculated incidence figures have been published from North America and Europe. There are a limited number of small paediatric studies from Asia, with one study from Africa and none from South America.[46-48, 51-53] On the data available, it would appear that IBD is more common in North America and Europe compared to Australasia (table 2.3). Within Europe there are marked differences in incidence between different countries. Even within a nation there are differences in incidence among the various regions as detailed in the study from Canada, reporting on variable incidence and prevalence among the five provinces with the same means of case ascertainment (table 2.4).[19]

Table 2.4: Incidence figures of CD and UC in children and adolescents (aged less than 20 years) among the various provinces in Canada (mean per 100,000 during 1998-2000)*.[19]

Provinces of Canada	CD	UC
Alberta	9.4	4.1
British Columbia	5.4	3.2
Manitoba	6.9	4.5
Nova Scotia	12.0	5.7
Saskatchewan	7.9	4.2

*Incidence figures extrapolated from the study and presented in the table.

There are suggestions from a limited number of studies of a north-south difference in incidence of IBD with a higher incidence in the north.[42, 54, 55] The European collaborative study on IBD (EC-IBD) revealed that the incidence of UC was 40% and CD was 60% higher in the northern European centres compared to the southern centres in those aged above 15 years of age, although some centres in the south had a higher incidence.[55] Interpretation of European studies revealed a higher rate of new cases of IBD in children from the northern regions of Europe (table 2.3), with the exception of Northern France, Spain and Croatia.[13, 26, 30, 41] It was interesting to note that this variation was due to CD and not UC, as suggested by a Scottish study demonstrating a significantly higher incidence of paediatric CD in the northern regions of Scotland with no differences evident in the incidence of UC.[56] Similar results were found in a French study demonstrating a north-south gradient for the incidence of CD, but not for UC, in a combined cohort of children and adults.[57] This variability has not been reproduced in other studies and hence the need for ongoing research.[26]

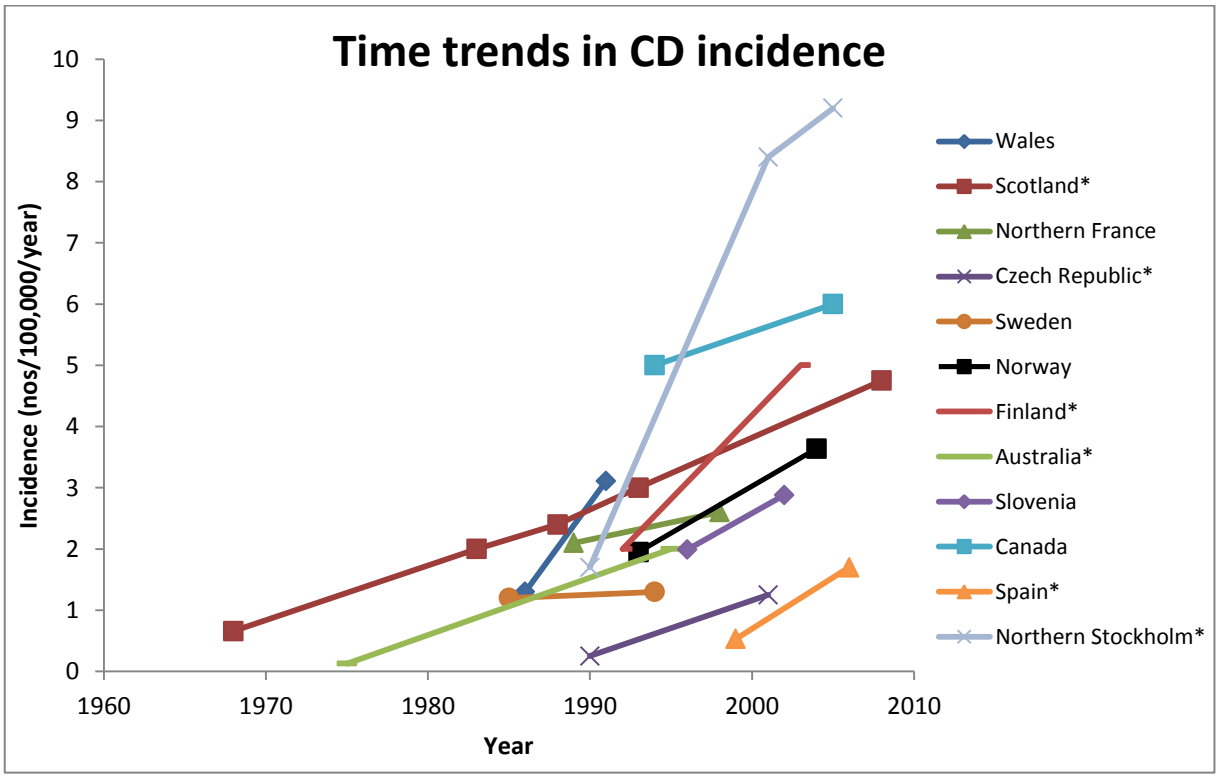
In areas of high paediatric IBD incidence there appeared to be a predominance of CD compared to UC with the exception of Finland where there was a predominance of UC.[31, 32]

In contrast, UC was predominant in Italy[34] and Poland[10] where the overall background incidence of IBD was low. This observation does not hold true for Australasia where the majority of children were diagnosed with CD, despite the overall incidence of IBD being low.[21, 49, 50]

2.3.2: Is the Incidence of Paediatric IBD Changing?

A review of various paediatric studies world-wide suggested that the incidence of IBD is increasing; mainly due to the increased incidence of CD, whereas the incidence of UC has remained relatively stable with some exceptions. Significant increases in the incidence of CD (figure 2.1) were demonstrated in Scotland (1968-2008),[39, 40, 58] Czech Republic (1990-2001),[9] Northern Stockholm, Sweden (1990-2001),[22] Finland (1987-2003)[31, 32] and Victoria, Australia (1971-2001).[21] In addition, increases in the incidence of CD, while not statistically significant, were reported for Wales,[43] Northern France[13] and South-Eastern Norway.[38]

Figure 2.1: Changes in the incidence of paediatric CD over time (values derived from various paediatric studies in which incidence figures were calculated at a minimum of two time points).[9, 13, 14, 21, 22, 31, 32, 38-40, 42, 43, 58]

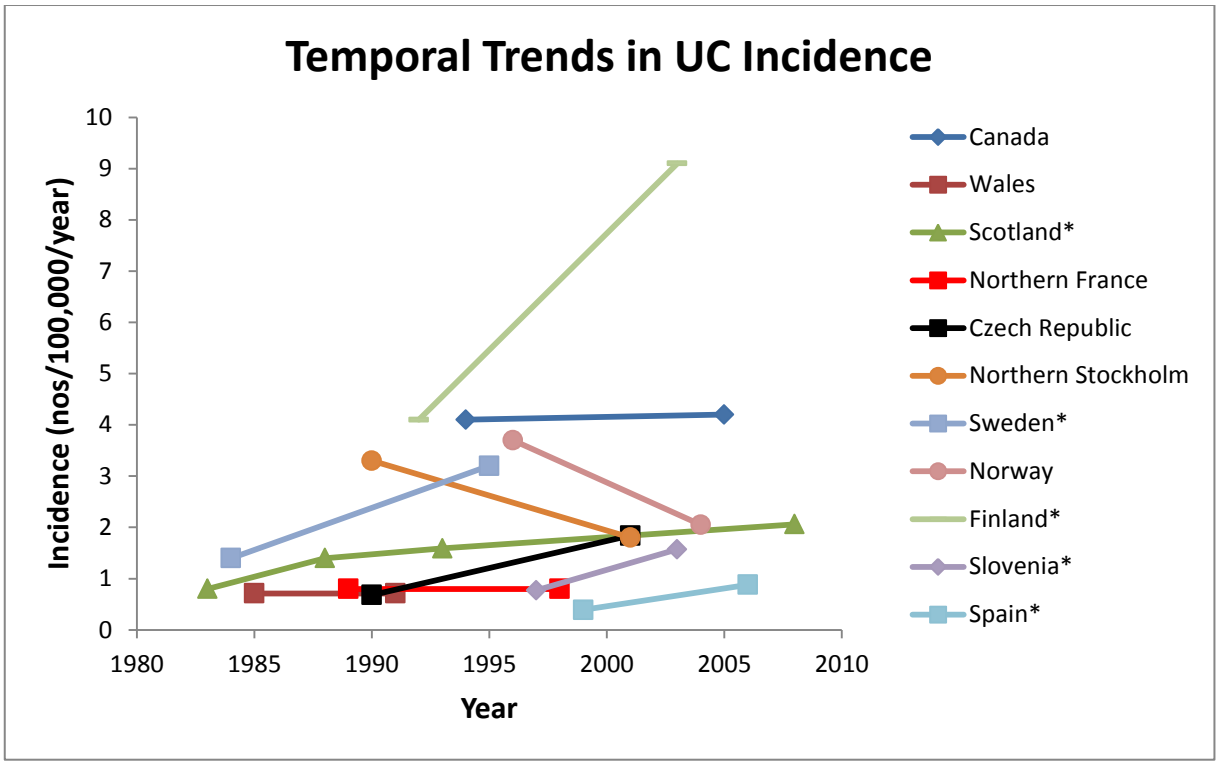


*significant change

In contrast, there has been conflicting variability in the incidence of paediatric UC over time (figure 2.2). There have been significant increases in UC incidence in Sweden (1984-1995),[14]

Scotland (1990-2008),[39, 40, 58] Finland (1987-2003),[31, 32] Slovenia (1994-2005)[59] and Victoria, Australia (1950-2009).[49] A non-significant rise in UC incidence was present in the Czech Republic (1990-2001).[23] The reported incidence of UC has decreased in South-Eastern Norway (1999-2004)[38] and Northern Stockholm, Sweden (1999-2001).[22] There were no changes in incidence of UC in Northern France (1997-1999)[13] and the Ontario province of Canada (1994-2005).[27]

Figure 2.2: Changes in the incidence of paediatric UC over time (values derived from various paediatric studies in which incidence figures were calculated at a minimum of two time points).[13, 14, 22, 23, 27, 31, 32, 38-40, 42, 58, 59]



*significant change

It has been suggested that the rise in CD incidence may be due to an increased frequency of upper gastrointestinal endoscopy at the time of diagnosis and better colonoscopic assessment of the entire colon with improved rates of terminal ileum intubation. Contrary to this suggestion, many studies have demonstrated that despite the rise in CD incidence, UC rates have remained stable or have risen during the same period, indicating an overall increase in IBD.[13, 14, 23, 31, 39, 43, 49, 59, 60]

In addition, several studies have suggested that most of the rise in CD has occurred in teenagers and not in the younger population.[14, 22, 38, 39, 61, 62] In contrast, the study by

Benchimol et al[27] from the Ontario province of Canada, demonstrated significant increases in the incidence of IBD in children aged 6 months to 4 years and 5 to 9 years. When stratified according to disease subtype, the significant increase was demonstrated only in children diagnosed with CD aged 5-9 years.

The epidemiological review of IBD by Loftus[63] highlighted the fact that developing countries with a low incidence of IBD, usually observe an initial increase in UC incidence, followed by a rise in CD incidence during which UC incidence plateaus. Whilst this observation was based on several adult studies, paediatric studies have shown similar trends. These trends have occurred in the Scandinavian countries, the United Kingdom and North America where earlier studies showed a predominance of UC, followed by a rise in the incidence of CD whilst UC remained relatively stable or decreased.[22, 38, 58] Italy had a low incidence of IBD earlier with a predominance of UC (52% of the IBD cohort) in children aged less than 18 years.[34] The incidence of IBD then increased significantly from 0.89 to 1.39 per 100,000 between 1996 and 2003 with an initial rise in UC, followed by a rise in CD incidence whilst UC remained relatively stable between 1998 and 2003.[34]

2.3.3: Differences between Urban and Rural areas

Differences in incidence figures between urban and rural areas have only been demonstrated in a few studies. This was the case in the study from Manitoba, Canada, where there was a greater incidence of IBD, especially CD, in a combined cohort of children and adults residing in Winnipeg (population of >50,000) compared to the rest of the province with a lower population during 1987-1996 (incidence rate ratio: 1.21; 95% CI: 1.00, 1.45).[64] The only paediatric study demonstrating a similar relationship was from Victoria, Australia, in which there was a significantly greater incidence of CD in children aged 16 years or younger from the city of Melbourne compared to the rest of the state during the period of 1971-2001 (incidence rate ratio: 1.66; 95% CI: 1.28, 2.16).[21] A recent systematic review and meta-analysis of all studies, both paediatric and adult onset disease, revealed that living in an urban area (population greater than 10,000) was associated with an increased risk of CD and UC.[65]

2.3.4: What Influence does Age have on the Incidence of IBD

Two large population based epidemiological studies have illustrated a peak incidence of CD in the 20-29 years age group, and 20-39 years age group in UC (figure 2.3 and 2.4).[7, 19, 66] Many reviews have ascribed a quarter of all IBD incident cases in children and adolescents. Recent studies have reported a lower proportion with approximately 10% of all CD and 5% of

UC diagnosed in those less than 17 years of age.[13, 53] In the Manitoba province of Canada, 13.1% of CD and 7% of UC were diagnosed in those less than 20 years of age.[7]

Figure 2.3: Incidence of IBD according to age at diagnosis in Manitoba, Canada (incidence values extrapolated from the study and then plotted).[7]

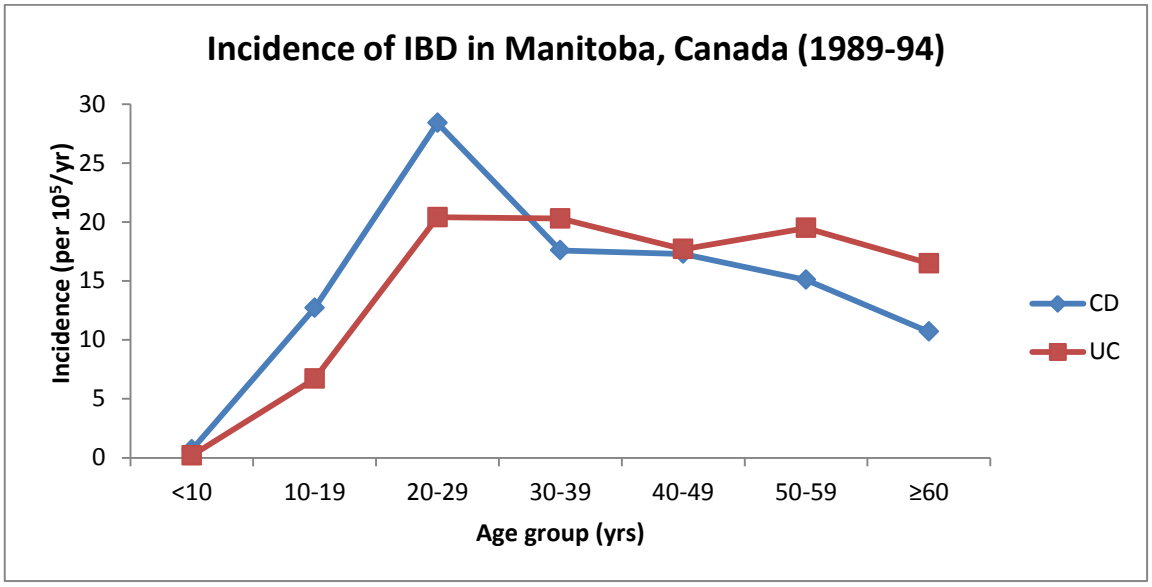
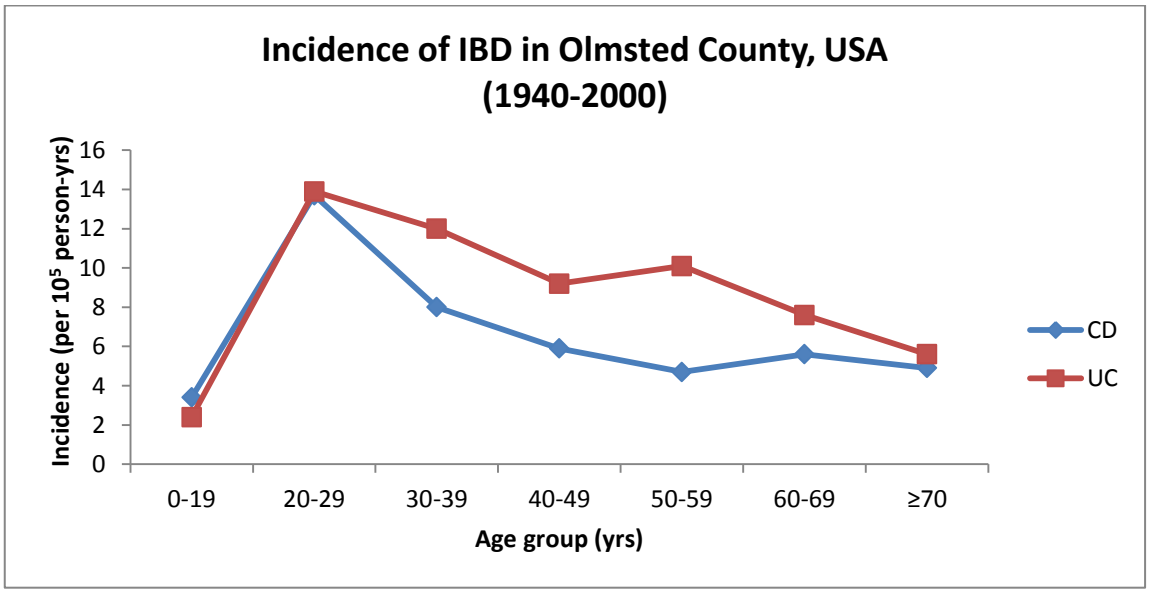


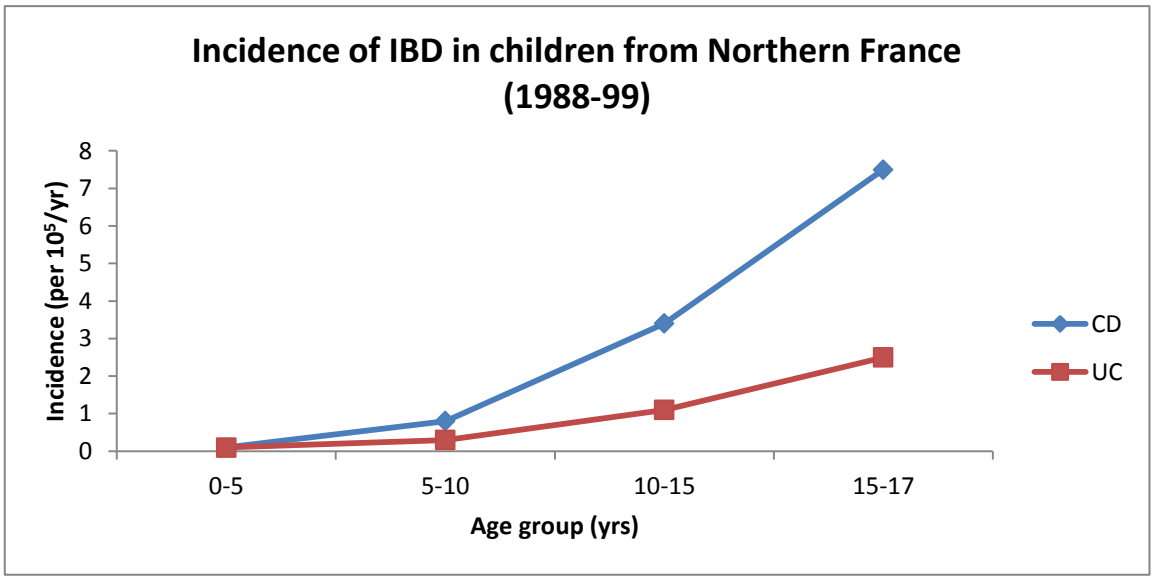
Figure 2.4: Incidence of IBD according to age at diagnosis in Olmsted County, USA (incidence values extrapolated from the study and then plotted).[66]



Within the paediatric population, the incidence of IBD increases from infancy to adolescence. Several studies have shown a marked rise in IBD from six to eight years of age, with a significantly greater increase in CD compared to UC and IBDU.[22, 25, 38, 67, 68] In the Wisconsin paediatric study, the incidence of IBD increased from <5 per 100,000 per year in those less than eight years of age to 13 per 100,000 per year by the age of ten years.[25] Other studies

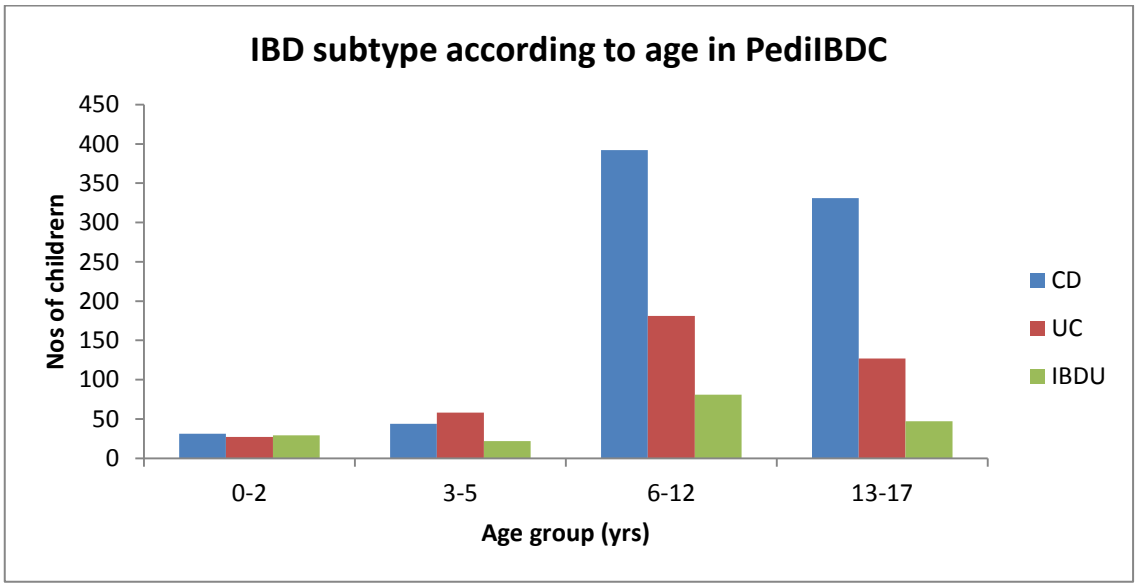
have shown similar increases in CD incidence from 0.1-1.2 per 100,000 per year in those children less than five years of age to 5.1- 9.4 per 100,000 per year in mid-adolescence (figure 2.5).[13, 15, 22, 38, 39] With regard to UC, the corresponding figures in those less than five years of age were 0.1 to 0.6 per 100,000 per year, increasing to 1.23 to 5.3 per 100,000 per year in mid-adolescence (figure 2.5).[13, 15, 22, 38, 39] The rise in incidence continues throughout adolescence into adulthood.[7, 19, 66] Thus, approximately 80% of children with IBD are at least ten years of age at the time of diagnosis, 4-15% are less than five years of age and 1% are less than one year of age.[13, 22, 68-70]

Figure 2.5: Incidence of IBD in children from Northern France during the period 1988-1999 (incidence figures adapted from the study and then plotted).[13]



This rise in incidence from six to eight years of age is greater for CD compared to UC.[25, 67, 68, 70, 71] This was highlighted in the North American Pediatric Inflammatory Bowel Disease Consortium (PediIBDC) study, which showed equal proportions of IBD subtype in those less than six years of age and then a significantly greater rise in CD in the older children (figure 2.6).[68] The proportion of IBDU can be as high as 30% in young children who are less than five years of age, decreasing to approximately 10% in adolescence and adults.[68, 72]

Figure 2.6: Number of children diagnosed with CD, UC and IBDU subtype according to age during the period of January 2000-November 2002 (figure derived from the values published in the study).[68]



The reported mean age at diagnosis in paediatric studies is frequently flawed and lacks clinical significance. The age distribution of IBD within the paediatric cohort is skewed towards adolescence with increasing incidence continuing into adulthood. Further, the reported mean ages are limited by the differing upper age ranges of the epidemiological cohorts between various studies. Currently, there is no consensus on the upper age for a paediatric cohort with variability between 15 and 18 years. Data acquisition is a major variable when patients are being looked after by paediatric clinicians versus adult based clinicians, and the adolescent age group is a period of significant overlap. Despite this, many paediatric studies have demonstrated that children with CD are diagnosed at an older age compared to UC and IBDU, explained by significant changes in disease subtype from eight years of age and the difficulty in differentiating the subtype in younger children with isolated colitis.[14, 15, 34, 70]

2.3.5: Duration of Symptoms prior to Diagnosis

There is marked variability in the duration of symptoms prior to diagnosis among the various studies and disease subtypes. The reported pre-diagnostic duration of symptoms is 3-13 months for CD, 2-11 months for UC and 4-14 months for IBDU.[13, 15, 34, 39, 61, 70, 73] Generally, children with CD presented after a significantly longer duration of symptoms compared to UC.[13, 29] There are a number of reasons for this variability. Firstly, the type of symptoms at disease onset may have impacted on time to diagnosis, with children presenting with subtle

symptoms such as mild abdominal pain or slowing of growth having a longer delay compared to presentation with rectal bleeding and diarrhoea.[70, 73] Secondly, some parents have difficulty in recalling the onset of subtle symptoms. Thirdly, younger children with subtle symptoms may present after a longer delay given their inability to articulate their discomfort.[34] Finally, parents and health professionals have become better at recognising IBD resulting in a quicker diagnosis.[61] Some symptomatic children may go unrecognised for a long period of time and then be diagnosed above the arbitrary age limit of the defined paediatric cohort, thus excluding them from the paediatric study and under-estimating the true incidence. Incidence reporting based on symptom onset may be more appropriate, but also may be limited by recall bias.

2.3.6: Does the Gender Distribution of IBD vary with Age

The gender proportion among children with IBD does vary, depending on differences in case ascertainment and the proportion of UC compared to CD. Generally, there is a male predominance among the younger children, especially those diagnosed with CD.[9, 22, 25, 27, 31, 34, 68, 74] With regard to disease subtype, most of the studies have demonstrated a male predominance (ratio of 1.2-1.8 compared to females) in those children diagnosed with CD.[6, 9, 22, 25, 27, 37, 39, 70, 75, 76] The reverse is true in newly diagnosed adults with CD, in which there are greater numbers of females.[6, 19, 20, 75, 77] This change in paediatric male predominance of CD to adult female predominance occurs at the time of late adolescence.[27, 76] In the paediatric study from Northern France, there was a significant change in the male to female ratio in the children with CD from 1.41 in those diagnosed prior to 15 years of age to 0.94 in those aged 15-17 years.[76] This change in gender predominance during mid-adolescence, may suggest that hormonal changes at the time of puberty may contribute to the onset of intestinal inflammation in response to environmental factors, thus predisposing women to the onset of CD. With regard to UC, there is no consistent trend in gender distribution among the various paediatric and adult studies.[6, 8, 9, 13, 14, 19, 25, 31, 34, 37, 39, 55, 66, 70, 75]

2.3.7: Impact of Ethnicity

Ethnicity appears to have an influence on the incidence of IBD in children. The incidence of IBD is increased in the Jewish community as shown in both adult and paediatric studies.[6, 78, 79] In the Greater Toronto Area of Canada, 20% of children diagnosed with IBD during 1980-1996 were of Jewish ethnicity which was six times greater than the 3.4% background Jewish paediatric population.[6] There are higher reported rates of IBD in Jews born and residing in

North America and Northern Europe (predominantly Azhkenazi Jews), compared to Ashkenazi Jews living in Israel.[79] The rates of IBD are even lower among Sephardi Jews and those born in North Africa and Asia.[78-88]

Most of the paediatric studies from the USA have shown no difference in the incidence among African-American children compared to Caucasian children with a few exceptions.[25, 68, 89] This lack of difference may be due to variation in access to health care. A study by White et al[90] reported that of the children diagnosed with IBD from six paediatric centres across North America (Pediatric IBD consortium), there was a significantly greater proportion of CD among African American children (78%) compared to non-African American, predominantly Caucasian, children (59%; $p<0.001$). In the paediatric study from the Texas Children's Hospital, the incidence of IBD was significantly higher in the Caucasian children compared to African American and Hispanic children during 1991-2002, but the proportion of CD to UC was higher in the African American (total cohort=36; 77.8% CD vs 13.9% UC) compared to Caucasian children (total cohort=205; 53.7% CD vs 39.5% UC).[62] In contrast, there is no difference in the incidence of IBD between Afro-Caribbean and Caucasian children from the UK and Ireland.[29]

Several studies have examined the epidemiology of IBD in South Asian immigrants to the UK and Canada. In the UK paediatric cohort, there was a significantly greater proportion of UC diagnosed in South Asian children.[29] Similar results were reported in a paediatric study from British Columbia, Canada, where South Asian immigrant children had a greater incidence of IBD (15.19 per 100,000 per year) compared to non-South Asian children (5.19 per 100,000 per year).[24] Unlike the prior UK study, South Asian children in British Columbia had an increased incidence of both CD and UC. This increased incidence contrasted with the lower rates in their parents' native country.

Studies have reported lower incidence of IBD in the Aboriginal Canadian population and among the indigenous Maori and immigrant Pacific Islanders of New Zealand.[50, 64, 91] At present, there are no paediatric studies from Australia comparing IBD incidence among the various ethnic groups.

2.3.8: Importance of Environmental Factors on the incidence of Paediatric onset IBD

Environmental factors do play an important role in the onset of IBD. It has been noted that when families migrate from a country of low to high incidence of inflammatory bowel disease, it is their children who gain an increased risk of IBD and not the parents despite similar genetics and ethnicity.[24, 29] Therefore, environmental influences probably have a greater impact on children during the time of maturation of their immune system, intestinal mucosal integrity and the bacterial flora within the gut. Some of these environmental factors will be discussed.

Several pre- and perinatal factors have been investigated as possible associations with conflicting reports, such as mode of delivery, maternal health, maternal smoking, maternal age and parity.[92] Breast feeding has been shown to protect against the onset of IBD in two systematic reviews.[93, 94]

There are conflicting reports on the associations between the number of household members, bedroom sharing, order of the child within the family, type of water used and pets.
Active or passive exposure to tobacco during the childhood years has generated variable results.[95-97] A recent study by Mahid et al[97] demonstrated that active smoking during childhood in Kentucky (US) was associated with increased risk of both CD and UC, but passive smoking was associated with CD.

Dietary intake may also play a part in disease onset. Having a diet high in meat, protein or n-6 polyunsaturated fatty acids may increase the risk of IBD, whereas a diet high in fruit and vegetables may be protective.[98-103]

There are conflicting reports on the increased risk of IBD in those who experienced gastroenteritis and/or exposed to antibiotics within the first five years of life.[92, 98, 104-113] An appendicectomy may be protective against UC, but increased the risk of CD within the first five years following surgery, with the highest risk within the first year.[114-116] One of the arguments in the case of CD is whether the appendicitis is actually part of the chronic inflammatory process and not truly acute. In addition, the bacterial flora may have been altered by the appendicectomy, influencing future risk of IBD.

2.4: Conclusion

IBD in children provides a unique opportunity to study a population in which environmental factors may modulate the immune maturation, intestinal mucosal lining and intra-luminal bacterial flora in a genetically predisposed individual, resulting in disease onset. Given that the incidence of IBD, especially CD is rising, these influences early in life may be contributing to this increase. Up till now, there has been variation in data acquisition among studies, thus resulting in differences in the incidence and limiting meaningful analysis between regions and time. Ongoing research needs to be population based and prospective with complete capture of all incident cases within the agreed age, and a uniform definition for the disease subtypes. Not only are there differences in incidence between childhood and adult onset disease, the diagnostic phenotype is equally important and will be discussed in the following chapter.

Chapter 3: Phenotype at Diagnosis of paediatric onset Inflammatory Bowel Disease

3.1: Introduction

Phenotype refers to the observable expression of a disease, which is dependent on the interaction between the underlying genotype and environmental factors.[117] It may include the age of onset of disease, gender predilection, symptoms and signs, anatomical disease involvement, laboratory markers, anthropometric parameters and disease behaviour. In some conditions, the phenotype is predictable and homogeneous based on the genetic abnormality or it may be complex with marked variability in expression. Even within the same disease subtype there may be marked variability.

IBD is heterogeneous with regard to disease subtype, presenting symptoms and signs, and anatomical involvement. Differentiating various IBD subtypes, such as CD, UC or IBDU may be difficult especially in the younger age group. In addition, phenotypic features of IBD are not static but dynamic and may change over time.

There are clear differences in the phenotype between childhood and adult onset disease, and within the paediatric population between the very young and adolescence.[67, 69, 71, 75, 118-120] There is no clear definition of early onset disease but several studies have used less than six or eight years of age.[25, 67, 68, 71, 75, 120] In the latest paediatric modification of the Montreal classification, early onset disease is referred to children diagnosed below the age of ten years.[121] The following literature review will discuss the phenotype of IBD in children, making comparison with adult onset disease and highlighting any age-related changes within the paediatric cohort.

3.2: Presenting Symptoms and Signs

The presenting symptoms and signs of IBD depend on the anatomical location, extent and severity of disease. Most children present with gastrointestinal symptoms, which includes abdominal pain, diarrhoea, rectal bleeding, weight loss and fever. The pooled results of children presenting with various symptoms and signs are shown in table 3.1.[6, 8, 25, 34, 70, 73, 122, 123] In UC, children are more likely to present with abdominal pain, bloody diarrhoea and/or chronic diarrhoea. The presenting symptoms are more heterogeneous in CD, with not only abdominal pain and chronic diarrhoea, but also weight loss, fever and perianal disease. Indeed, between 2 and 22% of children present with perianal disease, either fissures, tags,

fistula, abscesses and/or ulcers.[6, 34, 70] Other presenting symptoms in CD may include lethargy, anorexia, vomiting/nausea and oral lesions. The proportion of children presenting with extra-intestinal symptoms and signs are quite variable and difficult to compare among the various studies because of differing definition. Some studies report up to 35% of children presenting with extra-intestinal manifestations if fever, anorexia, malaise, weight loss, growth impairment and delayed puberty are included in the definition.[122] Children with CD are more likely to present with impairment in weight and height compared to UC.[70]

Table 3.1: Presenting symptoms/signs of IBD (percentage).

Symptoms	**CD (%)**	**UC (%)**	**IBDU (%)**
Abdominal pain	43-95	10-76	46-78
Diarrhoea	30-87	67-98	44-74
PR blood loss/bloody diarrhoea	14-60	46-97	22-84
Weight loss	43-92	20-55	17.4-31
Fever	10-48	4-34	11-13
Perianal disease	2.1-8 (fistula, ulcers or abscess), Up to 22 (fissures/tags)	2.7	5.3

In a study of children diagnosed with CD at The Hospital for Sick Children in Toronto (Canada) between 1980 and 1989, the majority (approximately 78%) had the classic presentation of abdominal pain, diarrhoea, weight loss and/or extra-intestinal manifestations.[6] On the other hand, 8.4% presented only with extra-intestinal manifestations, 3.7% with isolated perianal disease and 3.3% with growth failure.

Younger children, less than five years of age with CD are less likely to present with abdominal pain, lethargy and weight loss, and more likely to present with rectal bleeding compared to older children.[69, 71] Gupta et al[124] found that girls with CD had a significantly increased chance of mouth sores at presentation and interestingly increased risk of erythema nodosum or pyoderma gangrenosum, while boys had an increased risk of growth failure at presentation. Theses gender differences have not been reproduced in other studies. No significant differences have been demonstrated in clinical presentation among various ethnic groups.[24, 70, 89, 123]

3.3: Disease Distribution within the Gastrointestinal Tract

Not surprisingly, both UC and IBDU predominantly involve the colon. In contrast, CD can involve any part of the gastrointestinal tract from the mouth to the anus. The difficulty in comparing various studies is the differing reported classification of disease extent. For example, the division of CD involvement into small intestinal, large intestinal or combined small and large intestinal or more detailed division into terminal ileal, colonic, ileocolonic and upper gastrointestinal disease. Classification differences among studies are further complicated by differentiating caecal involvement from the rest of the colon, and including the jejunum as part of the upper gastrointestinal tract. With regard to UC, there are different ways of describing disease extent among the various studies with some combining sigmoid with rectal involvement (rectosigmoid). In addition, there are differences in the description of proximal colonic involvement with regard to the term extensive colitis versus pancolitis, depending on whether the disease is proximal to the splenic or hepatic flexure respectively.[121]

Recognising the need to standardise the description of disease location and indeed disease behaviour to achieve uniformity between studies, the Vienna classification was devised. This was further modified at the Montreal World Congress of Gastroenterology in 2005.[18, 125] The Montreal classification of CD (table 3.2) and UC (table 3.3) provides a framework for all researchers to describe disease extent. Although the Montreal classification of IBD was devised predominantly for adult onset disease, it was applicable to children. Further modification of the Montreal classification for children, highlighting their distinctive and unique phenotype has been another advance, the so called Paris modification (table 3.4/3.5).[121]

Table 3.2: The Montreal classification of CD.[18]

Age at Diagnosis (A)			
A1	16 years or younger		
A2	17-40 years		
A3	40years		
Location (L)		Upper GI modifier	
L1	Terminal ileum and/or limited caecal involvment	L1 +L4	Terminal ileum + Upper GI
L2	Colon	L2+L4	Colon + Upper GI
L3	Ileocolon	L3+L4	Ileocolon + Upper GI
L4	Upper GI*		
Behaviour (B)		Perianal disease modifier (p)	
B1	Non-stricturing, nonpenetrating (inflammatory)	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

*GI Gastrointestinal tract

Table 3.3: The Montreal classification of UC.[18]

Extent (E)		**Description**
E1	Ulerative proctitis	Limited to rectum
E2	Left-sided UC	Extends to distal of splenic flexure
E3	Extensive UC	Extends to proximal of splenic flexure
Severity (S)		**Description**
S0	Clinical remission	No symptoms
S1	Mild UC	≤4 bloody stools/day, no systemic symptoms/signs, normal haemoglobin (Hb)/ESR
S2	Moderate UC	>4 bloody stools/day, minimal signs of systemic toxicity
S3	Severe UC*	>6 bloody stools/day, pulse >90bpm, temp >37.5^{o}C, Hb<105 g/L, ESR>30mm/h (systemic toxicity)

*Included in this group is fulminant colitis which was separated in previous guidelines and is defined by ≥10 bloody stools daily, continuous bleeding, toxicity, abdominal tenderness and distension, requirement for blood transfusion and colonic dilation on plain abdominal films.

Table 3.4: Paris modification of the Montreal Classification of CD.[121]

Paris Classification	Description
Age at Diagnosis	
A1a	<10 years of age
A1b	10 to <17 years of age
A2	17 to 40 years of age
A3	>40 years of age
Disease extent[a]	
L1	Distal one third of ileum and/or limited caecal disease
L2	Colonic
L3	Ileocolonic
L4a	Upper gastrointestinal disease proximal to Ligament of Treitz
L4b	Disease involvement extending from distal to the Ligament of Treitz to the distal one third of the ileum
Disease behaviour[b]	
B1	Non-stricturing/non-penetrating (inflammatory)
B2	Stricturing
B3	Penetrating
B2B3	Both stricturing and penetrating
p	Perianal disease modifier
Growth[c]	
G_0	No growth delay
G_1	Growth delay

[a]Disease location of L4a and L4b can be classified with the L1-3.
[b]Perianal disease modifier (p) is still added to the behaviour as per the Montreal classification (table 3.2).
[c]Impaired growth defined by at least one of the following: diagnostic or subsequent height z-score significantly less than expected (difference between observed height z-score and predicted z-score using the mid-parental heights' formula is >2.0 or difference between observed height z-score and the pre-illness score is >1.0) or current height z-score significantly less than diagnostic z-score (reduction of ≥ 0.75).

Table 3.5: Paris modification of the Montreal Classification for UC.[121]

Paris classification	**Description**
Extent of colitis	
E1	Ulcerative proctitis
E2	Left-sided colitis (distal to splenic flexure)
E3	Extensive colitis (extending distally from hepatic flexure)
E4	Pancolitis (proximal to hepatic flexure)
Severity	
S0	Never severe
S1	Current or past severe disease[a]

[a]Severe disease defined by the Pediatric Ulcerative Colitis Activity Index (PCUAI) as ≥65[126].

3.3.1: Disease Extent in Crohn's Disease

Significant upper gastrointestinal tract disease (oesophagus to duodenum) has been reported in 10 to 50% of children diagnosed with CD.[21, 25, 34, 68, 75, 119] Isolated upper gastrointestinal tract disease at presentation is uncommon with rates of less than 5%.[34, 75] Up to 80% of children with CD may have mucosal or histological pathology detected on endoscopy, including oesophagitis, gastritis, gastric or duodenal ulcers, and/or duodenitis.[127, 128] Two studies, one from North America[119] and the other from Scotland[75] have demonstrated a significantly increased frequency of upper gastrointestinal involvement in children compared to adults. There are no age related differences in the frequency of upper gastrointestinal disease within the paediatric cohort.[68, 71, 75]

The anatomical distribution of CD in the children is presented in table 3.6. Approximately half of the children will be diagnosed with ileocolonic disease. In the pooled data of 1153 children published by Barton and Ferguson,[129] the distribution was 38% for small intestinal, 20.4% for large intestinal and 38% for combined small and large intestinal involvement. In comparison, the Pediatric IBD Consortium Registry from the USA with 600 children diagnosed with CD below 18 years of age, reported that 14.5% of the children had small intestinal, 24% had colonic, and the majority (61.5%) had combined small/large intestinal involvement at diagnosis.[124] In a paediatric cohort from the Hospital for Sick Children (Toronto, Canada), the most common site of disease was ileocolonic (42% of children), whilst 29% had terminal ileum(+/-caecum), 20% colonic, and 9% with jejunum/proximal ileum involvement.[6] The highest published frequency of ileocolonic involvement at diagnosis was 69%, reported from Northern France[76] and South-Eastern Norway.[11] In an Australian paediatric study from Victoria, up to 93% had colonic involvement, 57% had disease of the ileum and 45% had upper gastrointestinal disease in those diagnosed between 1991-2001.[21] In comparison, a New Zealand paediatric study demonstrated that 39% of children had ileocolonic involvement, 6% had isolated terminal ileal disease and 48% had isolated colonic disease.[50]

Table 3.6: Distribution of disease in children diagnosed with CD.

Study	Age Range	Isolated terminal ileum (L1)*	Isolated colonic (L2)*	Ileocolonic (L3)*	Upper GIT (L4)
Scotland[75]	< 17yrs	5.9%	36.3	50.5%	50.9%
Wisconsin, USA [25]	< 18yrs	25%	32%	29%	14%
Vancouver, Canada[118]	< 20yrs	21%	16.1%	57.1%	18.7%
Italy[34]	< 18yrs	18.6%	25.8%	55.15	10.7%
Central/Western Slovenia[59]	<18yrs	27%	32%	41%	12%
Northern France[76]	<17yrs	13.9%	16.7%	69%	36%
South-Eastern Norway[11]	<18yrs	8%	23%	69%	76%
New Zealand[50]	< 15yrs	6%	48%	39%	73%

*Presence or absence of upper GIT disease.

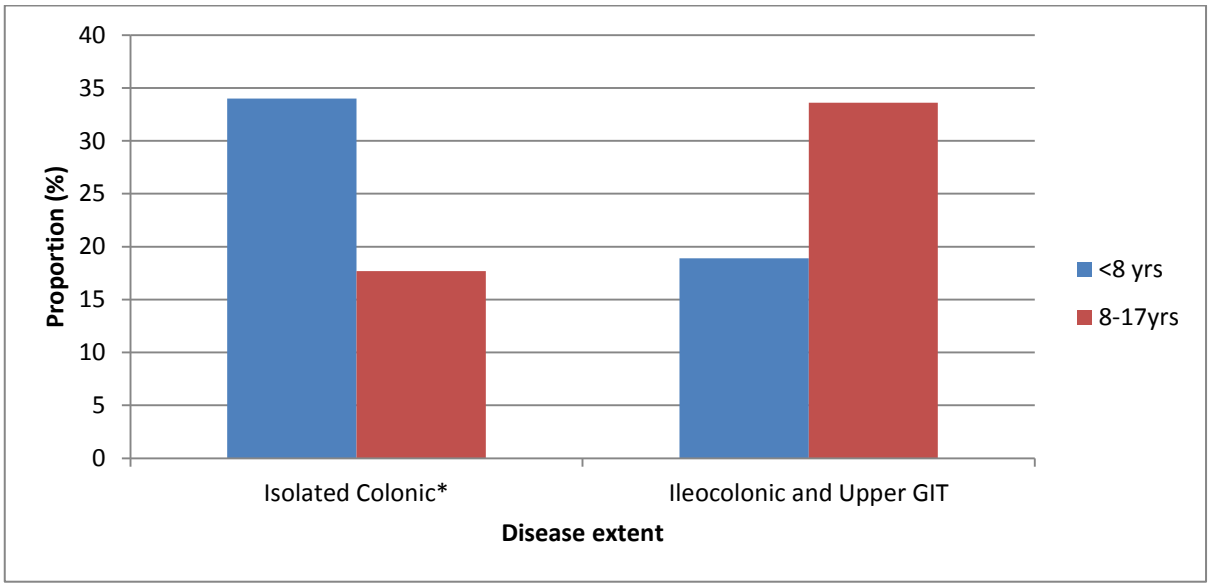
There are clear age related differences in anatomical distribution within the paediatric population. Children with CD onset below the age of 6-8 years have a significantly greater frequency of isolated colonic disease compared to older children (greater than 8 years of age).[67, 75] With increasing age into adolescence, there is an increasing frequency of extensive disease at diagnosis with small intestinal and/or ileocolonic involvement.[67, 68, 75, 130]

Of great interest, there are very clear and significant differences in disease distribution between children and adults. Adult patients present with less extensive disease. A Scottish study by Van Limbergen et al[75] made comparisons of disease phenotype between early and late onset paediatric disease and adult onset disease (figure 3.1/3.2). Children diagnosed with CD prior to eight years of age have a significantly greater frequency of isolated colonic involvement (L2), less ileal (L1 or L3) and less panenteric disease (L3+L4) involvement compared to older children. The overall paediatric population had a significantly greater panenteric (L3+L4), ileocolonic (L3 +/- L4) and upper gastrointestinal (L4) involvement and significantly less isolated ileal disease (L1 +/- L4) compared to adults. The study by Polito et al[119] from the USA demonstrated that patients diagnosed with CD at less than 20 years of age have a significantly greater frequency of small bowel and oesophageal/gastric/duodenal disease and significantly less colonic disease compared to those diagnosed at 40 years of age or older. In the study by Freeman,[118] the only difference in disease distribution between paediatric onset (< 20yrs) and adult onset CD was a significantly greater frequency of upper gastrointestinal involvement in the paediatric population.

However, most comparative studies demonstrate that children with early onset disease are more likely to have isolated colonic disease compared to older children. With increasing age up to mid-adulthood, the disease extends to involve the small intestine. Beyond 40 years of

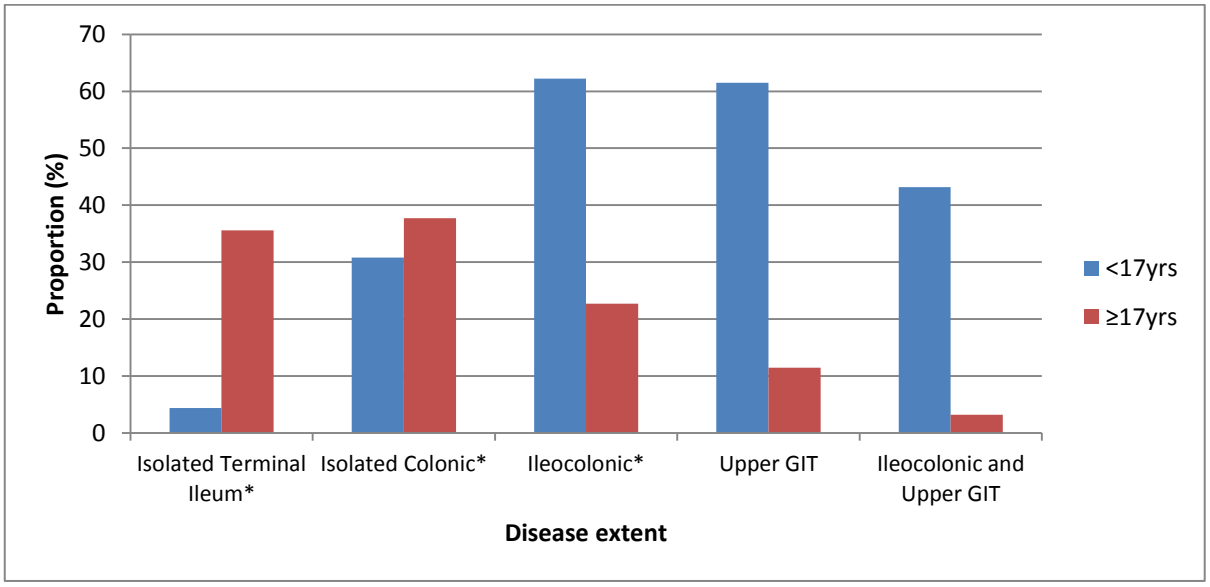
age, there is less upper gastrointestinal disease, less panenteric disease involvement and greater frequency of isolated colonic or isolated ileal disease[75, 118, 119, 131-133].

Figure 3.1: Disease distribution in Scottish children with CD.[75]



*No upper GIT disease (L4).

Figure 3.2: Comparison of disease distribution in CD between children and adults from Scotland.[75]



*Presence or absence of upper GIT disease (L4).

3.3.2: Disease extent in Ulcerative Colitis

Children with UC present mostly with disease extending proximal to the splenic flexure. Based on several paediatric studies, extensive colitis was present in 24 to 90% of children at diagnosis with the greatest proportion published from Wisconsin, Great Britain and Ireland.[6, 8, 9, 13, 22, 25, 34, 67, 70, 75, 122, 123, 129, 134]. The anatomical involvement among the various paediatric studies is presented in table 3.7. Recent studies have shown a greater frequency of extensive colitis, reflecting better colonoscopic assessment of the right side of the colon, whilst in the past this may have been missed by barium studies as the principle modality of investigation.

There are no differences in extent of colonic disease in UC between early and late onset paediatric disease, but there are marked differences in disease distribution between children and adults.[34, 67, 120] Children have more extensive disease and less isolated proctitis compared to adults.[8, 133, 135] Van Limbergen et al[75] in a study from Scotland demonstrated that children had a significantly greater frequency of extensive colitis (82.2%) compared to adults (47.6%). In contrast, the proportion of adults with isolated proctitis was significantly greater at 17% compared to 1.4% of children.[75] Other studies in adults have shown that between 14 and 37% presented with extensive colitis and 44 to 49% with proctitis.[8, 122, 133, 136]

Table 3.7: Disease distribution among various UC studies.

Study	Age	Extensive colitis (E3)	Left sided colitis (E2)	Proctitis (E1)
Mamula et al[120]	<5yrs	60%	40%	0
Paul et al[67]	<5yrs	67%	18%	15%
Paul et al[67]	5-15yrs	68%	18%	14%
Kugathasan et al[25]	< 18yrs	90%	10%	0
Sawczenko et al[70]	< 16yrs	90%	6%	4%
Barton et al[129]	< 17yrs	46%	27%	27%
Pooled data by Barton et al[129]	children	42.5%	35%	22.5%
Eidelwein et al[123]	<17yrs	75%	25%	
Auvin et al[13]	<17yrs	32%	57%	11%
Gower-Rousseau et al[134]	<18yrs	37%	35%	28%
Castro et al[34]	<18yrs	49%	44%	7%
Griffiths[6]	children	61%	26%	13%
Hyams[137]	<18yrs	41%	52%	8%
Langholz et al[8]	< 15yrs	29%		25%
Langholz et al[8]	>15yrs	16%		46%
Van Limbergen et al[75]	< 17yrs	82.2%	16.4%	1.4%
Van Limbergen et al [75]	Adults	47.6%	35.3%	17%

3.3.3: Disease Extent in Inflammatory Bowel Disease Unclassified

There are a limited number of studies describing the phenotype of IBDU because such children are excluded in some studies. IBDU tends to be diagnosed in younger children with a predominance of extensive colitis.[72, 130] In the study by Carvalho et al,[72] up to 80% of the children with IBDU presented with pancolitis and the remainder had left sided disease which usually progressed to pancolitis within 6 years. In contrast, the national paediatric IBD study from Italy reported that 43% of their children presented with extensive disease.[34] Reports of isolated proctitis in IBDU are scarce, most probably related to the fact that these children are usually labelled as UC and, in the presence of upper gastrointestinal disease as CD.

3.3.4: Perianal Disease in IBD

Perianal disease is usually found in CD and may consist of tags, fissures, fistulae, haemorrhoids, ulcers, strictures, abscesses and anal carcinoma .[138] Furthermore, the perianal fistulae may be complex and involve the vagina or bladder.[139] Complicated perianal disease is associated with significant morbidity, especially in teenage females, and may be resistant to therapy.

Perianal lesions may develop at any time during the disease course with 20-33% of perianal lesions developing prior to the diagnosis of intestinal Crohn's disease, 30-50% at the time of diagnosis and 20-50% developing later.[140-143] Non-healing perianal disease should raise the suspicion of CD, and prompt a full endoscopic evaluation of the upper and lower gastrointestinal tract.

One of the difficulties in reviewing the literature on perianal involvement in CD is that there is a wide variation in reported frequency of perianal disease as some authors excluded anal tags and fissures, whilst others included them. In addition, some studies did not specify the type of perianal lesion and reported the overall rate. The frequency of perianal disease reported in children and adolescents at diagnosis of CD is between 5 to 20% in most studies.[21, 34, 70, 71, 75, 123, 124, 144-147] Some paediatric studies have reported higher perianal rates of 23 to 50% at diagnosis.[50, 59, 89, 129, 148-150] Anal tags and fissures are the most common lesions with a reported diagnostic frequency of 5-34% in children with CD compared to perianal fistulae and/or abscess which are found in 5-10% of children[6, 25, 70, 76, 145, 146, 148]

There is no age related differences in the frequency of perianal disease between early and late onset paediatric CD. The study by Mamula et al[120] found that 34% of their children who were five years of age or younger had perianal disease. In comparison, despite the lower frequency reported by Gupta et al,[71] there were no significant differences between those aged 5 years or less (3.1%) compared to those who were aged 6-17 years (7.6%). There are no studies comparing perianal disease between children and adults. Between 36 to 46% of adults with CD may have perianal disease.[122]

There are some very interesting associations between perianal lesions and disease phenotype. Some studies have shown a male predominance of children and adults with perianal fistulae.[124, 141, 145, 151] Perianal disease has been associated with rectal and colonic inflammation in several paediatric studies.[129, 144, 148, 152] Two paediatric studies have demonstrated that the association was specifically between rectal inflammation and perianal fistula and/or abscess.[148, 152] This was highlighted in the adult study by Hellers et al,[151] where the frequency of associated perianal fistula was 12% in those with isolated small intestinal disease, 15% with ileocolonic CD, 41% with large intestinal CD but no rectal involvement, and 91% of those with large intestinal and rectal disease. In contrast, two other studies have not demonstrated this association.[145, 147] There are conflicting reports with regard to whether perianal fistulising disease is associated with intestinal fistula development, prompting their separation within the current Montreal classification.[18, 153, 154] Some studies have shown this association, with the presence of perianal fistula increasing the relative risk of intestinal perforation, especially in the presence of colitis.[154, 155] In addition, there is an association between perianal and orofacial CD, granulomatous or non-granulomatous.[156-159]

3.3.5: Orofacial manifestations of IBD

Orofacial lesions are common in children with CD. Orofacial lesions in CD may be part of the underlying pathophysiology (specific lesions) or secondary to nutritional deficiencies or side-effects of the medications.[160] They may include swelling of the lips, lip fissuring, buccal mucosal swelling with associated redness and /or cobblestoning, mucosal tags, deep linear recalcitrant ulcers or mucogingitivitis.[157] Orofacial granulomatosis is a clinical entity in which there is granulomatous inflammation of the oral cavity and face in the absence of gastrointestinal disease. There is debate about whether this disease is a separate entity or part of the CD spectrum.

The reported frequency of orofacial disease at diagnosis in children with CD is between 0.5 to 9%.[21, 70, 75, 156, 158] Higher frequencies of orofacial disease between 41 to 48% are reported when a dentist or oral surgeon conducts the oral assessment at diagnosis.[157, 161] Orofacial lesions may develop prior to any gastrointestinal symptoms or endoscopic evidence of disease in up to 60% of patients, or may present concurrently with gastrointestinal disease or following diagnosis.[162] In patients with isolated orofacial disease and no gastrointestinal symptoms or signs, up to half may have mucosal and/or microscopic evidence of gastrointestinal CD if endoscopic evaluation is undertaken.[163, 164]

Orofacial CD predominates in males, may present at a younger age with a longer duration of symptoms prior to diagnosis and associated with perianal disease.[70, 156-159, 161] Orofacial disease was shown to be associated with oesophageal and gastric inflammation in a retrospective study, but subsequently not reproduced in the prospective study by the same group.[156, 157, 161]

3.4: CD Behaviour

Children with CD usually present with an inflammatory process (Montreal classification B1; table 3.2) or with complicating behaviour, such as strictures (B2) or penetrating disease (B3) with perforation/fistula/abscesses.[18] It is not fully understood why children present with differing disease behaviour and what factors contribute to this. Anatomical disease location may influence disease behaviour as some studies have shown that ileal involvement is associated with strictures and, colonic disease is associated with inflammatory behaviour.[119, 165] Children may present with both intestinal strictures and an intra-abdominal fistula. In the Montreal classification, only one disease behaviour can be assigned, and thus a patient with both stricturing and penetrating, will be assigned as penetrating (B3).[18] This was based on an adult study showing that intestinal fistulae were present proximal to a stricture.[166] This association was refuted in a paediatric study where fistulae were not necessarily proximal or near a stricture.[167] Thus, the new paediatric Paris modification allows children to be labelled as combined stricturing/penetrating behaviour (B2B3; table 3.4).[121]

In the earlier Vienna classification of CD behaviour, patients with perianal fistula and/or abscesses were classified as penetrating disease behaviour (B3).[125] Studies have shown that the presence of perianal fistula/abscesses may not correlate with intestinal fistula and/or intra-

abdominal abscesses and so the presence of perianal disease is now indicated as the modifier "p" in the Montreal classification with no changes to the overall behaviour classification (table 3.2). [18] Disease behaviour may change over time and so inflammatory behaviour at diagnosis is considered interim for five years before it is assigned as definitive.[18]

The difficulty in comparing earlier studies was that disease behaviour was labelled according to the Vienna classification with perianal fistulae included as fistulising disease (B3), with reported frequency rates of 20 to 46% and inflammatory rates of 25 to 60%.[118-120, 125] Recent studies utilising the Montreal Classification, show that majority of children present with inflammatory disease behaviour with rates of 68 to 91%, 4.4-25% with stricturing (B2) and 4-18% with penetrating disease (B3).[59, 75, 76]

There are no age related differences in frequency of CD behaviour at diagnosis between early and late onset paediatric disease demonstrated so far.[68, 71, 75] Studies comparing paediatric and adult onset CD behaviour have provided conflicting results.[75, 118] Interestingly, age related differences have been shown in a handful of studies comparing patients with CD aged less than 20 years to those older than 40 years of age, with the younger cohort having a decreased frequency of inflammatory and increased frequency of penetrating behaviour. [119, 131-133, 168-170] Anatomical location of disease may have been a confounding factor in these studies with the younger cohort having a greater frequency of ileal disease, which is associated with complicating behaviour.[119, 131-133, 168-170]

3.5: Extra-intestinal manifestations (EIM) of IBD

The impact of IBD does extend beyond the gastrointestinal tract with extra-intestinal manifestations. There are difficulties in comparing studies because of a lack of a uniform definition for EIMs, leading to variable reported frequencies. Some researchers define orofacial CD as an EIM whereas others consider it as a separate entity or part of the gastrointestinal tract. Arthralgia was included as an EIM in some studies whereas others excluded it. Medication related side-effects have been included as an EIM in some studies but this is not truly related to the IBD and should be excluded. In addition, there is no clear consensus on what is a significant EIM. There are a limited number of studies describing EIMs in detail in both adult and paediatric studies.[171-173] There are no studies comparing the frequency and type of EIMs between children and adults. There was only one study comparing early and later onset paediatric IBD with regard to EIMs, and the only significant

result was that children diagnosed at six years of age or older had a greater frequency of EIMs compared to those less than six years of age (7 vs 3%; $p<0.05$).[173]

Reported frequency of EIMs at diagnosis varies between 6 to 47% among different adult and paediatric studies.[173-179] Stawarski et al[171] reported that 50% of children with UC and 80% with CD had at least one EIM. In comparison, Grossman et al[172] reported that 68% of children with IBD had EIMs but this was based on a study population of only 41 children. The most recent study by Jose et al,[173] based on a large cohort of 1649 children in the Pediatric IBD Consortium (consisting of six hospitals across USA), showed that 6% of children presented with an EIM at diagnosis, and the most common EIM was arthritis (26% of the EIM cohort). A similar study from North America, involving 19 centres throughout the US and Canada, found that 17% of all children aged less than 16 years presented with EIMs (children with IBDU were excluded).[179] Paediatric studies from Northern France reported that 23% of children with CD and 7% with UC presented with EIMs at the time of diagnosis.[76, 134] The frequency of EIMs is usually higher in CD compared to UC.[34, 76, 134, 174, 180] Within the cohort of UC, there are significantly higher rates of EIMs in those with extensive colitis compared to disease limited to the rectosigmoid.[174, 179]

EIMs can be grouped according to the involved organ or categorised according to their probable aetiology and behaviour with regard to the IBD phenotype. One group of EIMs are related to the colonic bowel activity, with correlation between the presence and severity of EIM and colitis activity. Colitis related EIMs involve the skin, musculoskeletal and ocular system.[175, 177, 179, 181] The second group of EIMs are related to complications or direct extension of the bowel disease. They are mostly related to small bowel disease in CD. They include malabsorption (including blood abnormalities such as anaemia and/or hypoalbuminaemia), genitourinary problems (renal stones, obstructive uropathy, enterovesical fistula), cholelithiasis and pancreatitis. The third group of associated EIMs include hepatobiliary disease, vascular, pulmonary, cardiac and neurological disease, where the disease process does not parallel that of the underlying intestinal activity.[175, 177, 179, 181] Therefore, control of the intestinal disease may not necessarily improve these EIMs. The final group of EIMs are iatrogenic, related to medications or surgery. Growth impairment, metabolic bone disease and pubertal delay are due to multiple factors including the underlying pathophysiology of IBD, malabsorption and adverse effects of medication.

3.5.1: Musculoskeletal EIMs

Joint involvement is the most common EIM with a reported frequency between 5 and 20%.[175, 181] In the study by Jose et al,[173] one third of the children diagnosed with IBD and an EIM (6% of entire IBD cohort) presented with arthritis. Review of the paediatric studies revealed that the frequency of arthropathy (including arthralgia) was between 1 and 22% at diagnosis, with most studies reporting a frequency of 10 to 20%.[6, 8, 21, 25, 34, 73, 76, 124, 134, 146, 182-184] Joint disease can be divided into peripheral and truncal arthropathy.

Peripheral arthropathy is more common and can be divided into type 1 and 2. Type 1 peripheral (pauciarticular) arthropathy affects less than five joints, usually large joints (knees, elbows and ankles), activity parallels the severity of colitis, usually acute onset and self-limited in duration lasting several weeks.[175, 181, 185] Type 1 arthropathy is usually associated with erythema nodosum and uveitis.[181] Type 2 peripheral (polyarticular) arthropathy affects five or more joints, usually small joints, activity does not parallel the bowel activity and the duration is prolonged over several months or years.[175, 181, 185] Type 2 arthropathy is associated with uveitis but not erythema nodosum.

Truncal (axial) arthropathy encompasses spondylitis and isolated sacroiliitis. The activity of axial arthropathy is independent of bowel activity. Spondylitis refers to inflammation of the vertebra, associated with HLA-B27 positivity and usually progressive.[175, 181] Sacroiliitis refers to inflammation of the sacroiliac joints which may be asymptomatic and detected on radiological examination.[181]

3.5.2: Hepatobiliary EIMs

Hepatobiliary EIMs are reported in 1 to 8% of children.[21, 25, 70, 76, 123, 134, 173, 183] Hepatobiliary abnormalities are a heterogeneous group, including abnormal liver enzymes with no specific aetiology, primary sclerosing cholangitis, non-alcoholic fatty liver disease, hepatitis (granulomatous, autoimmune, chronic active), cirrhosis, bile duct carcinoma, amyloidosis, hepatic abscesses and choleliathiasis.[173, 175, 186] Primary sclerosing cholangitis is the most common hepatobiliary abnormality at diagnosis.

Primary sclerosing cholangitis refers to inflammation of bile ducts that may involve intrahepatic and/or extrahepatic ducts. It is difficult to find an estimate of the frequency at diagnosis because studies usually consist of a small number of children with primary

sclerosing cholangitis/IBD and data collection may include EIMs following diagnosis. The reported frequency of primary sclerosing cholangitis either at or following diagnosis is 1-6% for IBD, 0.3-1% for CD and 2.8-6% for UC.[21, 34, 173, 179] Primary sclerosing cholangitis usually precedes the onset of IBD, more common in UC, associated with extensive colitis compared to left sided colitis or proctitis, male predominance and its activity is independent of the bowel activity.[175, 176, 179, 186] It has been reported that between 70 to 90% of patients diagnosed with primary sclerosing cholangitis will develop UC.[186]

3.5.3: Cutaneous EIMs

Skin lesions may present in up to 15% of IBD patients.[177, 181] Within the paediatric cohort, the reported frequency is between 2 and 16%.[6, 25, 70, 76, 123, 134, 173, 183] In the large Pediatric IBD Consortium, Jose et al[173] reported that 7.5% of children developed dermatologic lesions either prior to or following diagnosis with the most common lesion being erythema nodosum (5.4% of the cohort) followed by pyoderma gangrenosum (1.6%) and psoriasis (0.5%). In Northern France, 16% of children with CD presented with skin manifestations, and erythema nodosum was the most common lesion with a prevalence of 7%.[76]

The typical lesions of erythema nodosum are tender red nodules, usually present on the extensor surface of the lower extremities. It is commonly associated with CD, its presence parallels that of the bowel disease activity and usually associated with peripheral arthropathy, ocular EIMs and pyoderma gangrenosum.[175, 177, 179-181, 187] In two adult studies, erythema nodosum was present at a higher frequency in females.[176, 180]

Pyoderma gangrenosum usually begins as a red pustule or nodule that spreads rapidly to surrounding skin and then changes into a deep ulcer with irregular edges and purulent material which is sterile.[175, 181] It is usually found on the extensor surface of the leg but can be present on other parts of the body. It is usually precipitated by trauma including surgery and its activity does not always parallel the underlying bowel activity. Its presence may be associated with arthritis, erythema nodosum, uveitis, and isolated colonic disease in CD and extensive colitis in UC.[176, 180, 187]

Other less common cutaneous lesions include psoriasis, Sweet's syndrome, cutaneous metastatic CD, erythema multiforme and epidermolysis bullosa acquisita. Sweet's syndrome

is an acute neutrophilic skin condition which is characterised by red, tender nodules or papules affecting the upper limbs, face or neck.[186]

3.5.4: Ocular EIMs

Ocular EIMs are reported in 1 to 6% of children with IBD.[76, 123, 134, 173, 175-177, 179, 181, 183] The most common lesions at diagnosis are episcleritis and uveitis.

Episcleritis usually presents as redness of the sclera and conjunctiva with no visual problems and usually painless. Its activity parallels that of the underlying bowel disease.[181] Uveitis may present as eye pain, photophobia, visual disturbance or headaches.[181, 186] Uveitis refers to inflammation of the middle part of the eye, including the iris, ciliary body, choroid and retina. The reported frequency by Jose et al[173] and Hofley et al[188] in their paediatric studies was around 4%. In Northern France, the reported frequency of uveitis at diagnosis in children with IBD was 1-2%.[76, 134] Uveitis may present acutely or evolve slowly over time, its activity does not necessarily parallel the bowel activity, may be associated with arthropathy and/or pyoderma gangrenosum.[175, 181, 187, 188]

Other ocular lesions associated with IBD include conjunctivitis, orbital inflammatory disease, marginal keratitis, optic neuritis, ischaemic optic neuropathy and retinal vascular disease.[189]

3.5.5: Other EIMs

Renal abnormalities associated with IBD usually result from malabsorption with consequent dehydration. Increased urate or oxalate excretion in the urine and/or hypercalcaemia results in calcium oxalate or urate renal tract stones. Direct extension of the small bowel disease may result in obstruction to the renal tract (obstructive uropathy), fistula between the bowel and renal tract, and localised infective collections.[181] In the study by Jose et al,[173] 5.4% of the children had renal stones. Immune complex glomerulonephritis has been reportedly associated with IBD.

Pancreatitis may be associated with IBD, but it mostly occurs as a side-effect of medications such as sulfasalazine, mesalazine and thiopurines. Less commonly pancreatitis may result from pancreatic duct obstruction, due to duodenal CD or sclerosing cholangitis.[189] Metastatic CD is rare and it refers to granulomatous inflammation similar to that seen in the

gastrointestinal tract but involving mostly the skin, cheeks, genitalia (both males and females), lungs, pancreas, bladder and lower limb joints (ankles/knees).[181]

Cardiovascular EIMs include pleuropericarditis, cardiomyopathy, endocarditis and myocarditis.[175] Respiratory EIMs include decreased pulmonary function tests, pulmonary vasculitis, apical fibrosis, bronchiectasis, bronchitis, bronchiolitis, tracheobronchial stenosis and granulomatous lung disease.[175, 181] Children with IBD do have a tendency for inflammation of their arteries. There is an increased risk of thromboembolic events secondary to abnormalities in the coagulation pathway. Rarely, neurological disease may be associated with IBD due to malabsorption of vitamin B12 (neuropathy), extension of local bowel disease to the spinal cord (spinal abscess) or cerebral thromboembolism.[189]

3.6: Metabolic bone disease

Childhood is a critical period of bone development and modelling, dependent upon adequate nutrition, sunlight and physical activity. Bone mass and density is an active balance between bone resorption and formation. Reduction in bone density will predispose a child to a lifelong risk of fractures. Assessment of bone density is usually by means of dual energy x-ray absorptiometry (DEXA) scan. The scan analyses the total body, lumbar spine and/or femoral head. The results are expressed as t-scores which are the standard deviation scores compared to the reference values in young healthy adults or as the more clinically relevant, z-scores which is a comparison to that of age and gender matched healthy subjects. Decreased bone density is clinically important when the z-score is less than -1.[190] Interpretation of these results is not straight forward and need to be modified in the setting of delayed puberty and impaired growth.[190, 191] Thus, these scores should be reported in terms of height age or more appropriately bone age.

There are several studies investigating bone density in both adults and children with established disease and following exposure to systemic corticosteroids which may decrease bone density.[190, 192-195] Studies presenting data on bone density at diagnosis are few, but importantly may help in delineating the impact of IBD on bone health prior to medical intervention.

With regard to paediatric studies there is conflicting evidence of bone density changes at diagnosis. In a study by Sylvester et al,[196] there was no significant difference in the bone

density between children with CD compared to normal healthy children. In another study by Sylvester et al,[197] children with CD were found to have significantly lower total body and lumbar spine bone density z-scores at diagnosis compared to the healthy or UC cohort, and children with UC presented with no deficits. This decreased bone density in children with CD and not UC at diagnosis has been reproduced in other studies.[198-200] The reported frequency in CD of total body and lumbar spine bone mineral density z-score less than -1 was 28-43% and 41-56% respectively.[197, 198] The frequency of total body and lumbar bone mineral density z-score of less than -2 in CD was 6-9% and 12% respectively.[197, 198] Impairment in bone density may be due to malabsorption of calcium and vitamin D, malnutrition, decreased lean body mass, impaired growth, decreased physical activity, delayed puberty, amenorrhoea/menstrual irregularities, inflammatory cytokines (IL-6) and decreased biochemical stimulants for bone formation.[196-198]

3.7: Growth Issues in IBD

Childhood and adolescence is an important time for growth in terms of weight and height gain, increase of muscle mass and pubertal development. Growth depends on many factors including nutrition, hormones, onset and duration of puberty and genetic potential. In utero, there is a high velocity of growth, decreasing in infancy and becoming steady throughout childhood. Then a further peak in growth occurs at the onset of puberty. Girls generally gain most of their height in mid-puberty whereas boys increase their height in late puberty and over a longer period of time.

Growth may be described in terms of recorded weight, weight for height, body mass index (BMI), height and height velocity as a standard deviation (z-score) from a normal community database according to gender and chronological age. Ideally, absolute height and its z-score should be evaluated according to bone age since chronological age may not correlate with the true stage of pubertal development. In addition, IBD may be associated with pubertal delay.

It is important that sequential heights are measured and interpreted in terms of the child's ethnicity and parental heights. For example a child's height may be on the 3rd percentile on the growth charts and this may be interpreted as growth failure, but the parents' height may also be on the 3rd percentile and thus the child is following the family growth pattern. Another example may include a child's height being on the 50th percentile at consultation

which would be considered to be normal but if the earlier heights were at the 90th percentile, and then a significant drop in growth rate has occurred.

There are several reasons for growth impairment in children diagnosed with IBD. Growth impairment may be due to decreased oral intake, malabsorption, increased calorie requirements secondary to inflammation and a direct consequence of the inflammatory cytokines.[201] The duration and severity of disease may have an impact on growth.

The onset of CD is usually associated with an initial decrease in weight, followed by a decrease in height velocity either prior to or following diagnosis.[202] The study by Kanof et al[202] investigated changes in weight and height velocity in children prior to their diagnosis of CD and revealed three important facts. Firstly, half of the children underwent a slowing of their weight prior to the same occurring in the height velocity. Secondly, 78% and 88% of children had a slowing in their weight and height velocity respectively prior to diagnosis.[202] In the same study, 46% of children had a decrease in height velocity prior to the onset of intestinal symptoms.

Several studies have shown that children diagnosed with IBD, usually CD, have a significantly decreased weight at presentation.[70, 197, 203-210] Children diagnosed with UC generally do not demonstrate any weight faltering or loss, except in a handful of studies.[70, 204, 206] The range of weight z-scores at diagnosis is presented in table 3.8.[11, 70, 150, 197, 198, 203-206, 208-214] The frequency of children with a weight or weight for height z-score below -2 (failure) at diagnosis is reported in 11-27% and 5-11% of children with CD and UC respectively.[70, 204, 206, 210, 214] The study by Sawczenko et al[70] showed that significantly lower weight is associated with CD involvement of the jejunum and ileum. A French paediatric CD study by Vasseur et al[210] demonstrated that girls have a significantly worse weight z-score, and that a raised CRP above 10mg/L and stricturing disease behaviour (B2)was associated with lower weight and BMI z-score at diagnosis. In another paediatric CD study by Thayu et al,[203] there was no gender related differences in BMI z-score but girls had a significantly lower lean and fat mass compared to boys. ASCA positivity was associated with poorer weight z-scores at diagnosis in one study, independent of small intestinal disease.[215] There are no studies in UC identifying phenotypic features at diagnosis associated with impairment of weight or BMI.

Table 3.8: Reported diagnostic weight, height and BMI parameters in children with IBD.[11, 70, 150, 183, 197, 198, 203-206, 208-214, 216]

Parameter	CD	UC
Weight for age z-score	-1.14 to -0.26	-0.32 to 0.2
Weight for height z-score	-1.1 to -1	-0.5 to -0.4
BMI for age z-score	-1.37 to -0.66	-0.2 to 0.024
Height for age z-score	-1.11 to -0.28	-0.15 to 0.6

Height velocity is the ideal measure of linear growth but usually there is no previous record of height prior to symptom onset and presentation. Therefore, all studies report height z-scores at diagnosis. IBD does have an impact on height velocity, mostly in the case of CD.

Significantly lower heights at diagnosis were reported in various CD studies with z-scores ranging between -1.11 and -0.28 (table 3.8).[11, 70, 183, 197, 198, 203-206, 210-214, 216, 217] The frequency of height z-scores of less than -2 (failure) or less than the 3rd percentile at diagnosis of CD was between 5.3 and 19%.[70, 150, 183, 204, 206, 210, 213, 214, 216, 218] There has been a temporal trend of less children presenting with impaired growth as demonstrated in the study from the Hospital for Sick Children, (Toronto, Canada), where 22% of pre-pubertal (Tanner stage 1 or 2) children with CD presented with a diagnostic height less than -2 standard deviations during 1990-96 compared to 7% during 2001-06.[218] Impaired height in CD may be inversely associated with duration of symptoms prior to diagnosis.[70, 206, 211] It may also be associated with disease involvement of the oesophagus, jejunum and ileum.[70, 214] On linear regression modelling, the duration between symptom onset and diagnosis was independently associated with height impairment above that of anatomical disease involvement in children diagnosed with CD.[70] ASCA positivity was associated with a poorer height at diagnosis.[215]

On review of the literature, there are no studies that reported a significant impairment in height of children diagnosed with UC. Despite this, children with UC may demonstrate a slowing in their height velocity prior to diagnosis.[204] The study by Hildebrand et al[204] followed the growth of children diagnosed with IBD from birth to adulthood. They demonstrated that children with UC had a decrease in height percentiles within the year prior to diagnosis, which was in contrast to those with CD who had a longer period of five years, thus explaining why they presented with significant height impairment. In comparison to CD, the reported frequency of diagnostic height z-score below -2 at diagnosis in children with UC was lower at 2-5% (table 3.8) and there were no studies demonstrating phenotypic associations with growth.[70, 204, 206, 218]

3.8: Pubertal Changes

Puberty is part of the normal development of children into adulthood, beginning in the early part of the second decade of life, which is also the time of increased incidence of IBD. Puberty involves the acceleration of height, increase of muscle mass, growth of axillary and pubic hair, changing of the voice, body shape transformation into the adult frame, increase in testicular size in boys, and breast development and onset of periods in girls. Height acceleration occurs in mid-puberty in girls and late puberty in boys. The age of onset and duration of puberty depends on genetic factors, hormones, nutrition and the presence of disease.

The literature on puberty in IBD is scarce since it is poorly recorded. CD may affect the onset of puberty and the child's progression through pubertal development.[11, 198, 204, 219] In the study by Hildebrand et al,[204] the age at peak height velocity (representing mid-puberty) was delayed by greater than two standard deviations in 23% of children with CD. In another study, the age at peak height velocity was delayed in both boys (median delay of 0.45 years; range: 2.1, -1.56; p=0.004) and girls (median delay of 0.83 years; range: 1.7, -0.42; p=0.06) diagnosed with CD compared to the normal population.[220] Menarche may be delayed in girls with CD as demonstrated in the study by Ferguson and Sedgwick,[221] with 8/11 (73%) and 3/11 (27%) having onset of menarche after 16 and 20 years of age respectively. The only significant factors possibly associated with pubertal delay are the higher median erythrocyte sedimentation rate and lower BMI within 12 months prior to the age of peak height velocity.[220]

3.9: Laboratory Parameters

Laboratory abnormalities are common in children with IBD. The study by Mack et al[222] investigated the laboratory values of haemoglobin, erythrocyte sedimentation rate (ESR), platelet count and albumin in children with newly diagnosed IBD, stratified according to disease subtype and severity according to the physician global assessment. It was identified that the frequency of normal laboratory values decreased with increasing disease severity. Overall, 21% of children with mild CD had all four normal laboratory values compared to 2% with severe CD. With regard to UC, the frequency of all four laboratory values being normal was 54% in those with mild disease compared to none with severe disease. In addition, 22% of all children with CD and 14% with UC had abnormalities in all four laboratory values.

Another study revealed that a reduced haemoglobin and raised platelet count was the best at identifying children with IBD compared to ESR, c-reactive protein (CRP) and albumin.[223]

Anaemia is common in IBD at diagnosis with reported incidence of 23.8 to 75% in CD and 17.6 to 84% in UC.[34, 71, 182, 222, 224, 225] One study reported a significantly greater proportion of African American children diagnosed with IBD or CD in the US having a lower haemoglobin compared to the rest of the paediatric cohort.[90] The anaemia is usually microcytic and secondary to blood loss, chronic disease and iron deficiency as a result of decreased intake, malabsorption, and increased uptake by the inflammatory process. There may be macrocytic anaemia if there is disease involvement of the terminal ileum with subsequent vitamin B12 deficiency.

The platelet count at diagnosis may be raised as a result of inflammation with a reported frequency of 9 to 88% in CD and 20 to 70% in UC.[71, 182, 224, 225] Raised white cell counts were found in 25 to 70% of children with CD and 63% of children with UC in one study.[71, 182]

Other common inflammatory markers are ESR and CRP, which are also raised in IBD. The reported frequency of raised ESR at diagnosis was 75 to 85% in CD and 23 to 89% in UC.[71, 182, 224, 225] Ethnic differences were noted with a significantly greater proportion of African American children presenting with a raised ESR compared to the rest of the paediatric population.[90, 123] A raised CRP is usually found in 65 to 100% of children with CD and 60% with UC.[224, 225]

Albumin may be decreased in IBD, especially in CD, usually reflecting decreased protein intake and increased gastrointestinal losses as a result of small and large bowel disease.[11, 50, 208] The reported frequency of hypoalbuminaemia at diagnosis is 31 to 63% in CD and 15 to 26% in UC.[124, 182, 224, 225] The frequency of hypoalbuminaemia is greater in small bowel CD, and in girls with CD compared to boys.[124, 182]

3.10: Serology

The two important serological markers are antibodies to perinuclear anti-nuclear cytoplasmic antibody (p-ANCA) and to the yeast, anti-Saccharomyces cerevisisae (ASCA). Positivity for ASCA may indicate small intestinal CD and p-ANCA for colitis. There is ongoing controversy with regard to the clinical utility of these serological markers.

The combination of p-ANCA and ASCA has been investigated as a tool in differentiating between CD and UC, and defining the extent of disease. In the meta-analysis of adult and paediatric studies by Reese et al,[226] presence of a positive ASCA and negative p-ANCA has a sensitivity of 54.6% with a specificity of 92.8% for CD. In comparison, negative ASCA and positive p-ANCA has a sensitivity of 55.3% and specificity of 88.5% for UC. In the paediatric subgroup, the sensitivity and specificity of negative ASCA/positive p-ANCA for UC improved to 70.3% and 93.4% respectively.

There is a large variation in the reported frequency of positive ASCA and p-ANCA levels depending on the means of testing and the cut-off value for positivity.[227-229] The reported frequency of a positive ASCA immunoglobulin (Ig) A or G result in CD is between 40 to 86%.[227, 229-238]

Several associations between ASCA positivity and disease phenotype have been demonstrated in both paediatric and adult studies. ASCA positivity is more likely found in those diagnosed with CD involving the small intestine, either isolated or in combination with colonic disease.[229, 239-246] In the paediatric study by Russel et al,[237] oral CD and low albumin (<35g/L) were independently associated with ASCA positivity. There are several studies demonstrating an association between ASCA positivity with stricturing or perforating CD behaviour, independent of disease distribution.[229, 239-245, 247-249] Age at diagnosis may determine the frequency of ASCA positivity with <20% being positive when diagnosed at the age of 0-7 years compared to nearly 40% in those 8-15years at diagnosis.[246] This result may be influenced by the lower frequency of small bowel CD in younger children. Another study demonstrated age related differences in ASCA positivity, significantly higher frequency in those diagnosed below 13 years of age (73%) compared to the 13-40 years (59%) and over 40 years (29%) age group.[229]

In UC, the frequency of positive p-ANCA at diagnosis is 57 to 82%.[120, 226, 227, 234, 236, 238] Positive p-ANCA may be associated with pancolitis or left-sided colitis but not proctitis in children and young adults as demonstrated in the study by Zholudev et al.[238] Presence of p-ANCA may not be influenced by disease activity or age of onset.[238]

In CD, the reported frequency of positive p-ANCA is between 5 to 32%.[227, 229-231, 234, 236, 238, 246, 247] It is interesting that 60% of children with CD aged five years or younger at diagnosis have a positive p-ANCA, probably reflecting the fact that 89% of this cohort have isolated colonic involvement.[120] The p-ANCA positive CD cohort has been shown to be a distinct phenotypic group with predominance of isolated colonic disease and UC-like disease behaviour.[229, 234, 246, 247, 250]

The clinical utility of ASCA and p-ANCA in identifying a child with IBD has some merit. Instead, anaemia and/or raised ESR is more sensitive in identifying a child with IBD compared to a positive p-ANCA or ASCA (83% versus 60%).[251] In another study, the combination of anaemia, raised ESR and rectal bleeding was more sensitive in identifying IBD compared to p-ANCA and/or ASCA (86% versus 68%).[236]

3.11: Granulomata in CD

Granulomata result from a chronic inflammatory process stimulated by an offending antigen which is difficult to eradicate and the antigen is suspected to be either an intestinal bacteria or self-antigen.[252] The granuloma in CD consists of a microscopic aggregate of macrophages surrounding a central area where the presumed antigen is present, without any central necrosis (noncaseating). The macrophages are transformed into epithelium-like cells (epithelioid) and the lesion is surrounded by a rim of mononuclear leukocytes. In long-standing granulomata, there is a further surrounding layer of fibroblasts and connective tissue. The epithelioid cells may fuse to form larger cells with multiple nuclei and these are called giant cells.[252]

Granulomata are associated with CD but they may be present in UC adjacent to ruptured crypts.[17, 253] There is a marked variation in the reported frequency of granulomata among studies. The frequency of identifying granulomata is increased with increased number of biopsies from multiple sites, concomitant upper gastrointestinal biopsies, terminal ileum intubation and greater number of serial sections of each biopsy being analysed.[232, 254, 255] The size and depth of tissue analysed is important since the detectable frequency of granulomata is greater in resected specimens compared to endoscopic biopsies.[256-258] The study by De Matos et al[232] highlighted the importance of undertaking an upper gastrointestinal endoscopy and completing a full colonoscopy with intubation of the terminal ileum. In their paediatric cohort, 61% of children had granulomata detected at diagnosis, of which 13.4% were isolated to the upper gastrointestinal tract, 23.2% had granulomata only in the terminal ileum and

5.4% had granulomata in both upper gastrointestinal tract and terminal ileum.[232] Within this study cohort, if the diagnostic procedure was only a colonoscopy without ileal intubation, then 42% of the children with granulomata would have been missed and the reported overall granuloma rate would have been reduced from 61 to 36%, leading to possible misclassification.[232]

Reported frequency of granulomata at diagnosis in paediatric studies is between 19.7 and 67.2%.[11, 13, 71, 124, 232, 255, 256, 259-262] Despite one study demonstrating a twofold increased frequency of granuloma detection in children compared to adults, other studies have not demonstrated any age related differences between adults and children, early and late childhood onset and no gender related differences.[71, 124, 256, 260, 262]

The presence of granulomata in CD has been associated with gastritis, perianal disease and extensive disease involving upper gastrointestinal tract and both small and large intestine.[232, 263, 264] The study by De Matos et al[232] demonstrated a significant association between the presence of granulomata in children and, hypoalbuminaemia and ASCA positivity.

3.12: Familial Association of IBD

The frequency of a positive family history does vary as result of differences in which family members are recorded (1st degree or any family members), hospital versus population based studies and whether the recorded frequency is at the time of the index child's diagnosis or during the lifetime of the relatives.[265] Some studies have calculated a lifetime or age-related relative risk of IBD based on family members living to the age of 70 years.[84, 265]

The reported proportion of children diagnosed with CD and/or UC who have a positive first degree family history is between 2.7 to 12%.[11, 38, 53, 67, 119, 137, 150, 182-184, 266, 267] With inclusion of second degree family members, the reported frequency is between 11 to 35%.[22, 25, 59, 68, 89, 119, 120, 123, 208]

The life-time risk of IBD developing in a first degree relative of an index CD patient is 4.8-5.2% for non-Jews and 7.8% for Jews.[83, 84, 268] The equivalent lifetime risk of a first degree relative of a UC patient is 1.6% for non-Jews and 5.2% for Jews.[84] The relative risk of IBD in a first degree relative is 5-35 in CD and 10-15 in UC.[265] Among first degree relatives, the

greatest risk is among siblings followed by children of parents with IBD and then subsequent development in parents of children with IBD.

Monozygotic twins have a 1 in 3 lifetime risk of developing IBD if the other sibling has been diagnosed with CD, and a 1 in 5 lifetime risk of IBD if the other sibling has UC.[265] With regard to non-twin siblings, the lifetime risk of another sibling of an index CD patient is 5.1% for developing CD and 7% for IBD in the non-Jewish population whereas the risk of IBD in the Jewish population is 10.4-16.8%.[83, 84, 268] The risk of IBD in a sibling of a UC patient is 0.9% in non-Jews and 4.6-5.7% in the Jewish population.[83, 84] The relative risk of IBD in a sibling of a child with CD is 25-42 and UC is 8-15.[265]

The lifetime risk of IBD in non-Jewish children is up to 10.4% when one parent has CD and 6.2-11% when one parent has UC.[265, 269] The risk is greater in the Jewish population with reported risks of 7.4-15.8% when one parent has CD and 2.9-7.4% when one parent has UC.[83, 84] The lifetime risk to children is 1 in 3 when both parents have IBD.[265, 270] The relative risk of IBD in a child of a parent with CD is 2-30 and UC is 2-15.[265]

The lifetime risk of parents developing IBD when one of their children has the disease is 1.2-4.8% in both the Caucasian and Jewish population.[83, 84, 268] The relative risk of a parent developing IBD when their child has CD is 12-16 and UC is 8-19.[265]

These familial associations have highlighted a few interesting issues. Patients with a first degree family history of IBD are generally younger at disease onset. In the study by Heyman et al,[68] children with IBD who were 0-2yrs at diagnosis had a significantly greater frequency of positive first degree family history compared to older children, and this significant difference was also shown in the UC children. Also in the same study, the multivariate analysis revealed that a positive 1st degree family history was significantly associated with early onset IBD (<8yrs of age). Similar results were reported in another study in which the rate of a positive family history was greater in those younger than 5yrs of age compared to older children (26% vs 11%).[67] In a further study, the median age at disease onset for IBD was significantly younger in children with a first degree family history of IBD.[267] Others have challenged this phenomenon by suggesting that clinicians are more likely to make a diagnosis at a younger age when there is a positive family history. Given the limited time frame of studies, there may be a bias towards reporting severe familial IBD at a

younger age. Also, the incidence of IBD has increased over the last few decades in the paediatric population and thus studies may report a younger age at diagnosis in those with a positive family member, when there may be other factors contributing towards this observation.[271-273]

Studying families with IBD has generated some other interesting associations. There is a strong concordance for disease subtype among first degree relatives with reported rates of 75-100% in parent-child and sibling pairs.[265, 267, 271] In addition, some studies have shown concordance of disease extent in both CD and UC, and to a lesser degree CD behaviour among relatives.[265, 267, 274]

3.13: Genetic Impact on IBD Phenotype

Genetic abnormalities increasing the risk and influencing the phenotype of IBD have been a focus of research. There are many genetic mutations which have been identified but their significance in IBD needs further research.[275]

The first and most studied gene is the NOD2/CARD15 gene found on the IBD1 locus of chromosome 16. This gene is responsible for the transcription of a cytoplasmic receptor which is found on many cells including white blood cells and intestinal epithelial cells. This cytoplasmic receptor is involved in the recognition of bacterial cell walls resulting in activation of inflammation. Its frequency among CD populations does vary according to ethnicities with greater prevalence in Caucasian North American, European and Jewish patients compared to a lower prevalence in Asian, Arabs, Africans and African Americans.[276-278] The presence of one mutation increases the risk of developing CD by 2-4 fold and two mutations increases the risk by 17-44 fold.[277] These specific mutations do have a low penetrance given the fact that 70% of CD patients do not carry the mutation, and the background carrier rate in the general healthy Caucasian population is 1-5% with two mutations and 10-20% with one mutation. Presence of NOD2/CARD15 mutation in CD has been associated with ileal disease.[276, 277, 279, 280] Other associations with this mutation include earlier age of disease onset, complicated disease behaviour (especially stricturing disease) and positive ASCA results.[276, 277, 279, 281]

3.14: Conclusion

This review has highlighted the uniqueness of childhood onset IBD. There is a clear evolution of phenotype from early to late childhood and then into adulthood, most likely reflecting changes in the inflammatory response with age at the level of the mucosa. Given that disease is extensive in children, especially those aged over eight years, and its impact upon a child's schooling, bone development, growth, pubertal progression and psychological state, it is important to be aggressive in therapy. In describing the phenotype at diagnosis, hopefully therapy will be tailored to optimise disease control, minimising complications and improving disease course.

Chapter 4: Discussion of Disease Course in Paediatric onset Inflammatory Bowel Disease

4.1: Introduction

The description of a chronic disease, such as IBD, over time is referred to as the "natural course" or "natural history". Being aware of the natural course is important for both the physician and the child. The aim of diagnosis and management is to alter the course of IBD such that the child will have no symptoms, halt the progression of disease and hopefully avoid complications. Accordingly, there is nothing "natural" with disease course when medical therapy is initiated and/or surgery is undertaken. It is proposed that the temporal description of IBD should be referred to as "disease course" or "disease history".

What is the goal in altering the disease course? Should the goal be resolution of IBD, with the prospect of ceasing medications in the long-term or control of disease with medical therapy? Generally, the aim of medical intervention is to control the disease with complete resolution of the inflammation.

The next dilemma is the best means of assessing disease course. Should this be based on subjective clinical symptoms and signs? What is the best evaluation of symptoms, avoiding inconsistencies among different children, their families and treating physicians? There are other measures of disease course, including corticosteroid use and efficacy, hospitalisation, changes in anatomical extent and disease behaviour, surgery, growth and bone development.

Finally, the other important issue is whether a person's disease course can be predicted at diagnosis by their phenotypic features. If this is possible then physicians may tailor therapy to maximise a good outcome. In the following discussion, both potential influencing factors at diagnosis and disease course will be presented.

4.2: Disease Course according to Clinical Symptoms and Signs

IBD is usually characterised by periods of disease activity with clinical symptoms interspersed by periods of inactivity (remission). There are several measures of disease activity according to clinical symptoms, such as the general physician global assessment, Montreal classification of UC severity, or more specifically the paediatric UC activity index (PUCAI).[18, 126, 282, 283] PUCAI was developed as an assessment tool for UC in 2007 (table 4.1).[126]

Objective measures of disease activity may include laboratory investigations, faecal measures of inflammation, imaging and endoscopic evaluation with histological assessment. The paediatric CD activity index (PCDAI) utilises both clinical symptoms, examination findings and laboratory values in assessing disease activity.[282] The PCDAI was developed and validated in 1991 (table 4.2 in Appendix A).[282] PCDAI is less reliable in assessing changes in disease activity over a few weeks because of the height and laboratory component which may take longer to respond to therapy. Description of disease activity according to symptoms may be hampered by the subjectivity of the patient and assessing clinician. The other flaw with the above measures is that they provide a snapshot at one point in time. These indices are useful in research, providing uniformity in disease activity description.

Table 4.1: Paediatric Ulcerative Colitis Activity Index (PUCAI).

	Score
Abdominal pain	
No pain	0
Pain can be ignored	5
Pain can not be ignored	10
Rectal bleeding	
None	0
Small amount only (<50% of stools)	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
Consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
Nocturnal stools (any episode that awakens the person)	
No	0
Yes	10
Activity level	
No limitation	0
Occasional limitation of activity	5
Severe restricted activity	10
Total score of PUCAI (0-85)	

PUCAI severity score:

- <10 (no activity)
- 10-34 (mild activity)
- 35-64 (moderate activity)
- >64 (severe activity)

4.2.1: Clinical Activity of CD over Time

Clinical activity following diagnosis is dependent upon the choice of therapy and the disease response. Induction therapy consist of either corticosteroids, enteral nutrition, methotrexate and/or biological agents (infliximab) for moderate to severe disease, based on clinical symptoms and signs, anatomical extent, laboratory and anthropometric parameters, as well as the routine practice of the physician.[284-286] In mild Crohn's colitis, 5-aminosalicylates may be the first choice. Reported short-term clinical remission rates in children diagnosed with CD vary between 60 and 98% within the first three months following initiation of systemic corticosteroids or exclusive enteral nutrition, with no differences between the two therapies.[285-293]

Beyond the first three months following initiation of therapy, clinical symptoms may vary according to initial response to therapy and whether maintenance therapy, such as immunomodulators has been started. The paediatric study by Griffiths et al,[217] described a one year response rate of 14% of children having no symptoms with normal laboratory markers, 54% having mild symptoms but not requiring corticosteroids, 23% having intermittent relapses requiring corticosteroids or enteral therapy, and 9% having chronic severe disease. The abstract by Critch et al[294] demonstrated that 60% of children were asymptomatic or had mild symptoms and 40% had moderate/severe disease at one year following diagnosis. In the same study, a significant relationship was demonstrated between the diagnostic PCDAI score and clinical activity during this follow-up period.

Following the initial therapy for CD, most children would maintain remission with intermittent relapses requiring treatment with corticosteroids, enteral therapy or biological agents. The study by Griffiths et al[217] demonstrated that within the first five years following initial therapy for CD, a third of children experienced mild symptoms only, in which no systemic corticosteroids were needed, another third had repeated exacerbations requiring corticosteroids but then went into definite clinical remission and 17% had chronic severe symptoms with no remissions despite corticosteroid treatment. The retrospective longitudinal paediatric study by Gryboski et al[182] found that the average number of clinical recurrences was 1-3 per year over a mean period of 6.5 years. The same study demonstrated that the number of exacerbations was significantly greater in those with persistent ileocolitis for two years following diagnosis.[182] However, medical management has changed since this study with early use of immunomodulators and the introduction of biological agents. Over the

long-term, 50% of children with CD will be in remission at any particular point in time and up to 75% of children will experience relapses within five years following diagnosis.[8, 36]

Absence of symptoms may not reflect resolution of endoscopic (mucosal healing) and/or histological inflammation (histological/deep tissue remission).[295-300] Therefore, the therapeutic goal should be mucosal healing and/or histological remission which have been shown to reduce the risk of subsequent disease recurrence, complications, hospitalisation, systemic corticosteroids and surgical resection in CD.[301-307] Overall, there are no features at diagnosis predictive of disease course, except for severe endoscopic lesions at colonoscopy associated with a higher risk of penetrating complications and surgical resection.[308]

4.2.2: Clinical Activity of UC over Time

Therapy in UC is dependent upon the extent and severity of colitis. Distal disease is usually treated with topical 5-aminosalicylate and/or corticosteroid, whilst more extensive disease is treated with oral 5-aminosalicylates and/or systemic corticosteroids. In addition, 5-aminosalicylates or sulphasalazine may be the initial therapy in mild severity, whereas systemic corticosteroids are used in moderate-severe disease.

In UC, clinical remission is achieved in just under half of the children within the first month of induction therapy, followed by remission rates of 70% and 85% within three and six months respectively.[137, 287, 309] A study by Hyams et al,[137] demonstrated that children presenting with a disease duration of six months or less prior to diagnosis were more likely to achieve clinical remission within three months compared to those with protracted disease(73% versus 50%; $p < 0.03$), but there were no differences at six months. Within the same cohort of children presenting with moderate-severe activity, those aged less than ten years were less likely to achieve clinical remission within the first six months compared to older children (68% versus 84%; $p < 0.03$).[137] These predictors of clinical response have not been reproduced in a recent study.[309]

Within any year following diagnosis in a cohort of children with UC, half will be asymptomatic, a third will have chronic intermittent symptoms, 4-8% will have continuous symptoms requiring long-term corticosteroids and the remainder may require a colectomy.[137, 310, 311] In the study by Stordal et al,[36] two thirds of children had experienced relapses within

the first five years following diagnosis. Between 28-40% of children are at risk of a severe disease episode during their childhood.[312, 313]

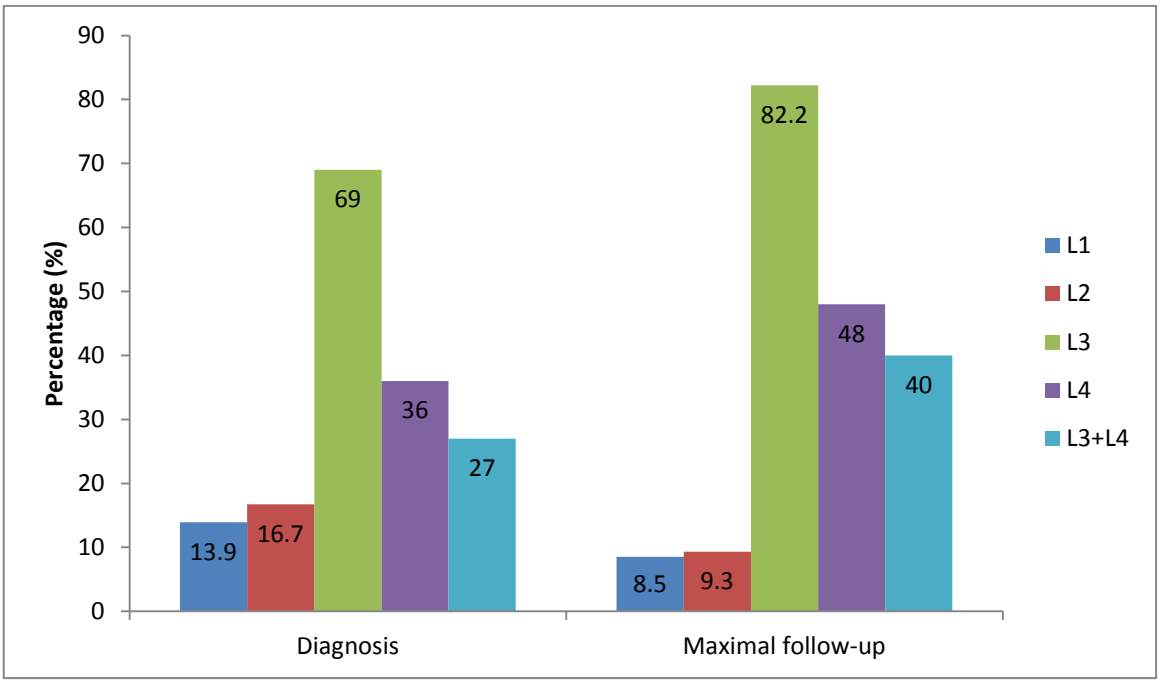
Similar to the situation in CD, resolution of symptoms may not reflect endoscopic and/or histological improvement. Thus, the therapeutic goal should be mucosal healing and/or histological remission, which is associated with improved outcomes.[301, 302, 306, 314] The only predictor at diagnosis of disease course is severe endoscopic lesions on colonoscopy, associated with non-response to medical therapy and increased risk of surgery.[315, 316]

4.3: Changes in Anatomical Disease Extent over Time

4.3.1: Crohn's Disease

In children the extent of anatomical disease may increase following diagnosis. In the Scottish paediatric cohort, 39.1% of children with limited disease at diagnosis experienced disease extension when followed for at least two years.[75] Over two thirds (68%) had disease extension from terminal ileum (L1) or isolated colonic (L2) to ileocolonic (L3) disease, whilst 26.8% developed upper gastrointestinal tract involvement (L4).[75] Similar findings were demonstrated in a French paediatric study, where 31% of children had extension of disease over the median follow-up period of 84 months (figure 4.1).[76] The proportion of children with maximal disease extent (ileocolonic with upper gastrointestinal disease (L3+L4)) increased from 27% at diagnosis to 40% ($p<0.01$) during the follow-up period. Other studies have shown that children tend to develop ileocolonic disease following diagnosis.[8, 182]

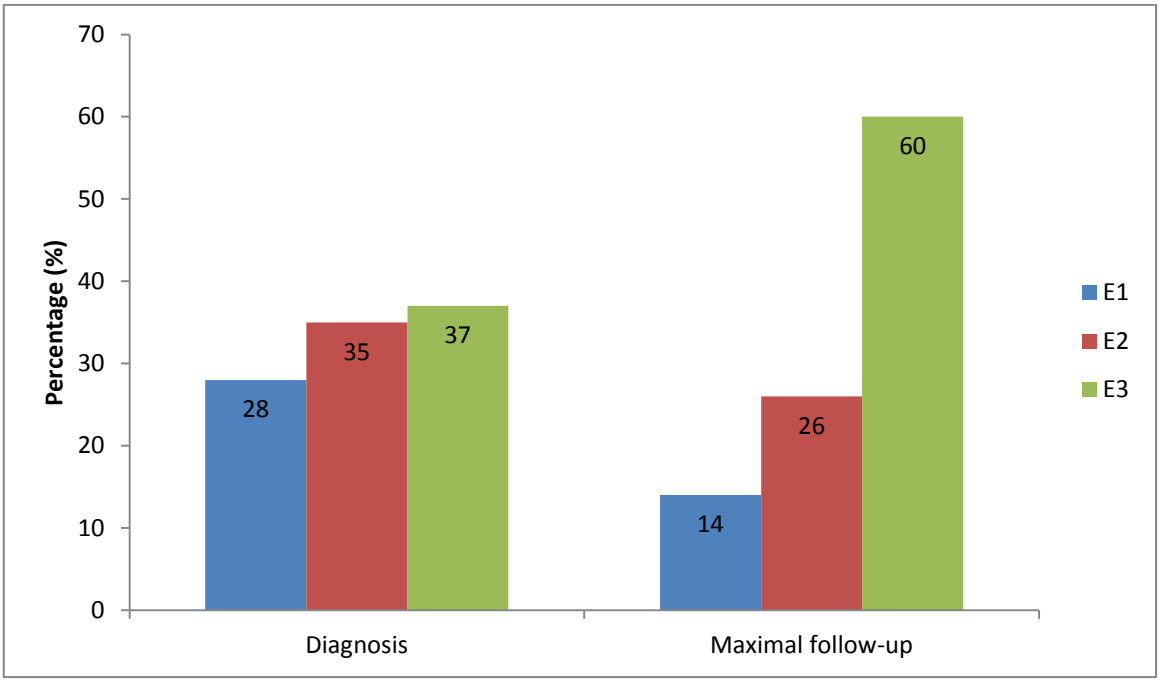
Figure 4.1: Disease extent in 281 children diagnosed with CD.[76]



4.3.2: Ulcerative Colitis

The majority of children diagnosed with UC present with pancolitis or extensive colitis (disease involving the colon beyond the splenic flexure). Those children presenting with proctitis or left sided colitis, approximately half will have extension in colonic involvement over time.[75, 134, 137, 184, 310, 317] With regard to proctitis, the risk of disease extension is approximately 25% and 70% at 3 and 15 years respectively following diagnosis.[8, 310] The French study by Gower-Rousseau et al,[134] demonstrated that half (49%) of the children with proctitis (E1) or left sided colitis (E2) at diagnosis underwent disease extension when followed for at least two years (figure 4.2). The same group identified that children with prolonged symptoms prior to diagnosis (>6 months) and/or positive first degree family history of IBD had a significantly greater risk of disease extension. In the Scottish study, 46% of the children presenting with distal disease developed extensive colitis over the follow-up period.[75] Children with proctosigmoiditis who had proximal extension to extensive colitis, have a more severe and active disease course with a high incidence of intestinal and extra-intestinal complications.[317] Of course, it should be emphasised this was before the era of increased immunomodulator usage and biological therapy.

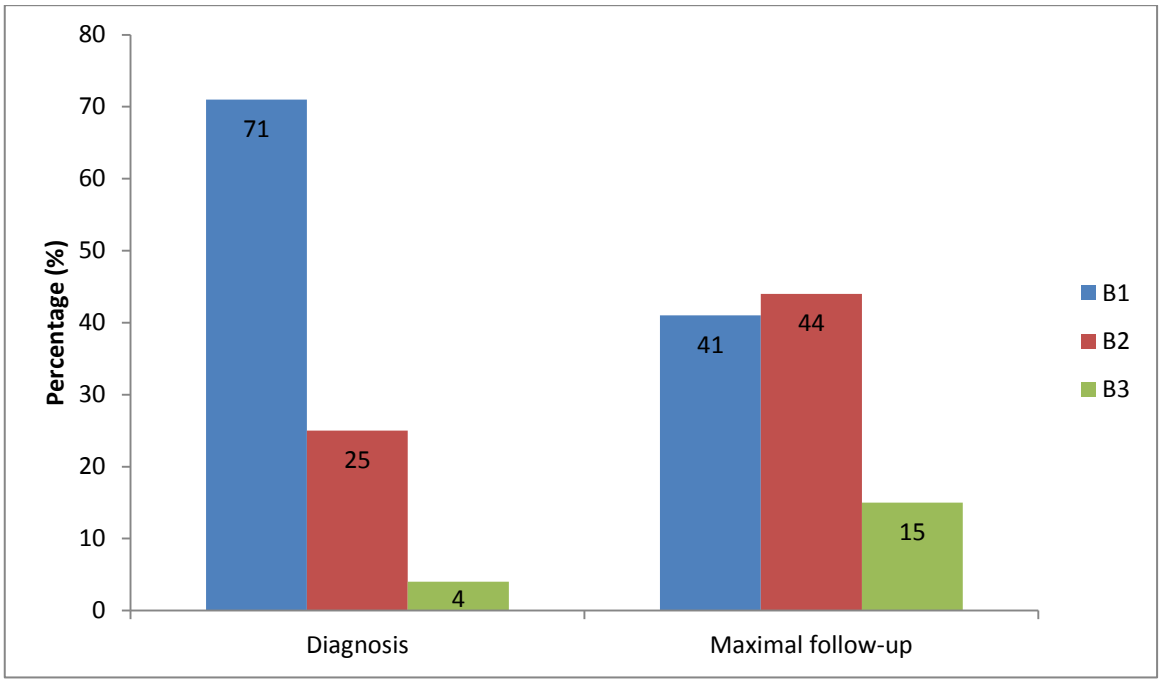
Figure 4.2: Changes in disease extent in 113 children with UC followed for at least 2 yrs.[134]



4.4: Changes in the Behaviour of Crohn's Disease

In children with CD, there is a predominance of inflammatory disease at diagnosis with rates of 70-90%.[75, 76, 318] Following diagnosis, there is an increase in complicating behaviour, either stricturing or penetrating disease, with reported rates of 17.9-59%.[75, 76, 169, 249, 318] In a paediatric study from Northern France, 71% of children had inflammatory behaviour (B1) at diagnosis, of whom 32% developed stricturing disease (B2) and 11% developed penetrating complications (B3) over a period of at least two years (median follow-up of 7 years; figure 4.3).[76] In the Scottish paediatric study by Van Limbergen et al,[75] the proportion of children with stricturing behaviour (B2) rose from 4.4% at diagnosis to 12.9% at maximal follow-up of at least four years following diagnosis. Similarly, the frequency of penetrating intestinal complications rose from 4.4% at diagnosis to 11.4% at maximal follow-up.[75] The study by Gupta et al,[169] based on a multi-centred US paediatric cohort, demonstrated that the cumulative incidence of complicating behaviour (including perianal penetrating lesions) was 13%, 26.7% and 37.9% at 1, 5 and 10 years respectively following diagnosis. Within the same cohort, the cumulative incidence of stricturing disease was 5.5%, 13.6% and 20.5% and penetrating complications (including perianal lesions) was 8.2%, 17.1% and 24.5% at 1, 5 and 10 years respectively.[169]

Figure 4.3: Changes in disease behaviour of 404 children with CD followed for at least 2 years.[76]



There are several factors at diagnosis which may predict a child's progression to complicating CD behaviour. Disease of the terminal ileum is usually associated with stricturing/penetrating disease and isolated colonic CD with inflammatory behaviour.[75, 169] Age at diagnosis may also play a part with older children (6-17 years of age) having a more complicated disease course with significantly greater risk of abscesses and fistulae compared to younger children.[71] A specific mutation in the CARD15 gene (3020insC mutation) may be significantly associated with CD stricturing behaviour.[319] Immune reactivity to several microbial antigens such as *Saccharomyces cerevisae*, *E.coli* outer-membrane porin C, *pseudomonas* fluorescens CD-related protein and anti-CBiR1 (antiflagellin) have been associated with both an increased risk of complicating behaviour and a shorter time to the development of the complication.[230, 248, 317] The number of positive serological tests and/or magnitude of the titres may be directly associated with both increased rates and shorter interval to stricturing or penetrating disease behaviour.[231, 249, 318]

4.5: Change in Diagnosis

Initial classification of IBD in children may be difficult, especially in the young. This is due to the fact that children below the age of eight years are more likely to present with isolated colonic disease, prompting a diagnosis of UC or IBDU.[67, 68, 120, 130] In addition, the classical differentiation between CD and UC has become complicated due to the fact that children with

UC may have gastritis, rectal sparing, backwash ileitis, periappendiceal and caecal inflammation in the absence of continuous colitis, which in the past would have been labelled as CD.[17]

Between 6-18% of children diagnosed with either CD, UC or IBDU may be reclassified later as a result of disease extension, changes in behaviour or histology as a result of subsequent endoscopic biopsies or intestinal resection.[14, 22, 31, 36, 183] Children with an initial diagnosis of IBDU are more likely to be reclassified, with 19-55% being labelled as CD or UC within two years.[14, 31, 68, 72, 120, 183] Serological markers at diagnosis of IBDU may help in predicting disease reclassification. Children with ASCA positivity/p-ANCA negativity at diagnosis predicted future classification to CD in 80% of cases and ASCA negativity/p-ANCA positivity was predictive of UC in 63.6% of patients.[320] Reclassification is least likely in CD compared to UC.[22, 31, 68, 183] Failure to thrive in young children with isolated colitis may be predictive of CD or IBDU.[120]

4.6: Efficacy of Response to Systemic Corticosteroids as a Predictor of Disease Course

Researchers and clinicians have also tried to describe disease course according to response to systemic corticosteroids. Description of corticosteroid use encompasses the duration and number of courses, and efficacy. Short-term response has been consistently described in terms of resolution of symptoms (complete or partial remission/response, and no response) within the first 30 days and/or three months. Corticosteroid efficacy over the longer term has been classified as completely "responsive" when symptoms resolve and the child was able to come off corticosteroids, "dependent" when remission occurred but there was recurrence on lower doses or upon cessation, and finally "refractory" when remission was not achieved or high dose was required for remission, leading to second line therapy and/or surgical resection. Corticosteroid efficacy has frequently been assessed at the end of the first year following diagnosis in several paediatric studies. There are slight differences in the definition of the above terms among the various studies, especially corticosteroid responsiveness. Several paediatric studies have described corticosteroid "responsive" as being able to be weaned off the corticosteroids, may have had an additional course but off corticosteroids with complete or partial resolution of symptoms at one year following diagnosis.[76, 134, 287, 288, 321] Another research group defined corticosteroid "responsive" as receiving one course of induction corticosteroids and maintaining improvement in symptoms at one year without further courses, and if a further course of corticosteroids was required with resolution of symptoms

then they were classified as "dependent".[288, 309] Description of corticosteroid response may be influenced by concomitant use of immunomodulators and/or biological agents, which may have been initiated because of disease severity or lack of initial response to corticosteroids. The study by Markowitz et al,[288] clarified this point by reporting the frequency of children with CD who responded to an initial course of corticosteroids and were in complete or partial remission at one year without a further course of corticosteroids and need for infliximab or surgery. The cohort of children treated with corticosteroids are usually those presenting with moderate-severe disease, who are likely to have immunomodulators started early following diagnosis, impacting upon the one year corticosteroid efficacy.[76, 134, 293, 309, 322]

4.6.1: Describing Disease Course of CD according to Systemic Corticosteroid Efficacy

Systemic corticosteroids induced complete resolution of symptoms in approximately 60% of children within 30 days, whilst 8-12% were non-responsive.[287, 322] In the study by Markowitz et al,[288] corticosteroids induced complete remission in 60% of children within three months, whilst 17% were non-responsive. At one year following the first course of corticosteroids, 50-60% of children will have complete/partial resolution of symptoms whilst not on corticosteroids, 14-45% will be corticosteroid dependent and 13-29% will be corticosteroid refractory and require surgery or biological therapy.[76, 287, 288, 322] With regard to the Markowitz et al study,[288] 46% of children had complete/partial resolution of symptoms following their initial course of corticosteroids without requiring a further course within the first year.

The frequency of corticosteroid refractoriness was higher at 27% in the Olmsted County[287] study compared to 5% reported from Northern France,[76] probably related to the fact that the Olmsted County study spanned between 1940 and 2001, predating the introduction and early use of immunomodulators and biological agents. Recent studies have reported that 61% of French children[76] and 81% of North American children[288] were started on immunomodulators during the first year following diagnosis and initiation of corticosteroids.

Two studies have identified predictors of corticosteroid efficacy. In the study by Markowitz et al,[288] a decrease in height percentile by at least one major channel below pre-illness percentile was associated with corticosteroid refractoriness and dependency. The presence of ileal disease (isolated ileal or ileocolonic) at diagnosis compared to isolated colonic or upper gastrointestinal disease was associated with corticosteroid dependency.[322]

4.6.2: Describing Disease Course of UC according to Systemic Corticosteroid Efficacy

In children with UC, complete clinical remission should be achieved in 50-63% within 30 days following the initiation of corticosteroids, whilst 8-21% may be unresponsive.[287, 322] In the study by Hyams et al,[309] 60% of children achieved complete resolution of symptoms and 12.9% were non-responsive at three months following the introduction of corticosteroids. At one year following the initial course of corticosteroids, 50-60% of children will be in complete or partial remission and not on corticosteroids, 14-45% will be corticosteroid dependent, and 5-29% will have failed corticosteroids and needed surgery or biological therapy.[134, 287, 309, 322] In the studies by Hyams et al[309] and Gower-Rousseau et al,[134] 86-91% of children were started on aminosalicylates and 25-61% commenced azathioprine or 6-mercaptopurine during this first year.

The frequency of corticosteroid refractoriness among children at one year from the Olmsted County was 29% compared to lower rates from the other studies, probably due to the fact it spanned from 1940 to 2001, and predated immunomodulators and biological agents, and the current practice of introducing such maintenance therapy within the first few weeks following diagnosis.[287]

4.7: Disease Course according to the Introduction of Immunomodulators/Biological Agents

The various immunomodulators used in IBD include thiopurines (azathioprine/6-mercaptopurine), calcineurin inhibitors (cyclosporine/tacrolimus), methotrexate and the biological agents (infliximab/adalimumab). These medications are usually used at the onset in moderate-severe disease where the potential for relapse may be high, the disease is resistant to initial induction therapy of corticosteroids or enteral nutrition, or when relapses occur within a short period of time. Therefore, disease course may be described in terms of immunomodulator use. The limitation in using this as a descriptive measure is that there will be a proportion of children started on immunomodulators early to prevent future relapses, who may not necessarily needed it. Thus, it will be an error to categorise these children as having a severe disease course.

4.8: Describing Disease Course according to Hospitalisation

A limited number of studies report hospitalisation in children, with varying descriptions. Some studies discuss hospitalisation in terms of the number of admissions, total duration over

the study period or mean duration per year. The need for hospitalisation is dependent upon the disease extent/severity, response to medical therapy and whether surgery is indicated. There is no dispute about the impact of hospitalisation upon the child in terms of their psychological wellbeing, lack of education, risk of infection and complications, as well as the stress upon the rest of the family.

4.8.1: Duration of Hospitalisation

No significant differences in the duration of hospitalisation between CD and UC were apparent in most studies, except for the study by Gryboski.[182, 323] Gryboski[182] reported that the mean duration of hospitalisation within the first two years following diagnosis was significantly shorter in children (aged ten years or younger) with UC (10 days) compared to those with small bowel (12.3 days), ileocolonic (28 days) or colonic CD (20 days), within the small cohort of 40 with CD and 30 with UC. Beyond the two years there were no significant differences.[182] Heaton et al[323] reported the mean hospitalisation duration in 2006 was 5.63 and 6.66 days for children with CD and UC respectively.

Children with CD presenting with stricturing and/or penetrating complications are more likely to require hospitalisation, as they may require fasting, prolonged intravenous antibiotics, total parenteral nutrition or enteral nutrition and surgery.[76] In the study by Gryboski,[182] children with CD involving their colon, isolated or combined with ileal disease, experienced a significantly longer mean duration of hospitalisation compared to those with isolated terminal ileum disease. In the case of UC, children do not require a hospital admission unless they develop severe colitis/toxic megacolon or acute haemorrhage.[134]

Other reported associations have come from single studies. The study by Heaton et al[323] demonstrated that children aged 0-5years of age with CD and 11-15 years of age with UC required a significantly longer mean duration of hospitalisation. In the study by Gryboski,[182] the mean yearly hospitalisation duration gradually decreased with time following diagnosis.

The number of hospital admissions for CD and UC remained stable between 1994 and 2004 among children living in Ontario, but the age-adjusted odds for hospitalisation was greater in 2001-2004 in both disease subtypes.[324]

4.9: Need for Surgery

4.9.1: Surgery in Crohn's Disease

The indications for surgery in CD include medically resistant disease and/or complications, such as strictures and perforation. Surgery is not curative, as disease may recur in other regions of the gastrointestinal tract. It may induce a prolonged period of clinical remission, promoting growth, pubertal development, improved bone density and attendance at school. Surgery in CD may include resection of bowel, open drainage of an abscess, closure of a fistula and any extra-intestinal complication within the abdominal cavity. The insertion of a gastrostomy or perianal surgery will not be discussed.

The risk of intra-abdominal surgery increases with disease duration, probably related to an increasing frequency of complications. The reported risk of intra-abdominal surgery is 5.7-7% within the first year, 11.6-30% after three years, 17-50% after five years and 30-50% after ten years (table 4.3).[75, 76, 149, 183, 230, 266, 324-328] This wide variation in surgical rates between studies are due to differences in management among centres and over time, the introduction of immunomodulators/biological agents over recent times and the earlier use of such medications during the disease course. The study by Lindberg et al[14] demonstrated a decrease in surgical rates for CD from 37.7% (1984-90) to 17.6% (1990-95). Similarly, there was a significant decrease in the three year surgical (intra-abdominal/resection) rates in children from Ontario between 1994-1997 and 2001-2004 (18.8% vs 13.6%).[324]

Table 4.3: Intra-abdominal surgical rates in children with CD following diagnosis.

Authors	Country	Year	1yr	3yr	5yr	10yr	Overall rate (mean/median period)
Castile et al[146]	US	1950-73					67% (8.8yrs)
Langholz et al [8]	Denmark	1962-87					13% (yearly). 47% (20yrs).
Barton et al [129]	Scotland	1968-83					57.4% (7.05yrs)
Sedgwick et al [328]	Scotland	1968-83			50%		60.3% (7.05yrs)
Patel et al [327]	US	1968-94		28.8%	47.2%		46% (3.8yrs)
Griffiths et al [329]	Canada	1970-87					32.4%
Besnard et al [326]	France	1975-94					30% (3.5yrs)
Gryboski[182]	US	1977-90					42.5% (4yrs)
Baldassano et al [330]	US	1978-96					23.4% (4.3yrs)
Freeman et al [266]	Canada	1979-1998			39.7%	50.9%	26.8% (2yrs) 56.3% (12.2yrs)
Vernier-Massouille et al [76]	France	1988-2002	7%	20%	34%		44%(7yrs)
Ba'ath et al [331]	UK	1994-2002					21%
Leonor et al [149]	Canada	1994-2003					17.5% (3.27yrs)
Newby et al [183]	UK	1997-2003	4.9%				11.6% (3.4yrs)
Mesker et al [325]	Netherlands	1998-2007			28%		
Gupta et al [230]	US	2000-03	5.7%		17%	28%	
Benchimol et al [324]	Canada	1994-2004			15.7%		
Van Limbergen et al [75]	Scotland	2002-08			20.2%	34.5%	17.1%

Predicting surgery at diagnosis is important so that early aggressive medical therapy can be instituted. The study on risk factors for initial surgery by Gupta et al,[230] demonstrated that being female, poor growth at diagnosis, raised white cell count, hypoalbuminaemia and ASCA positivity was significantly associated with increased risk of surgery. Children aged 3-12 years or those with fever at diagnosis had a decreased risk of surgical resection.[230] Endoscopic findings of deep and extensive ulcerations covering more than 10% of at least one segment of the colon was associated with an increased risk of surgery.[308] The presence of positive antibodies to microbial antigens, such as ASCA, *E.coli* outer-membrane porin C, *pseudomonas* fluorescens CD-related protein and anti-CBiR1 (antiflagellin) was associated with increased surgical rates.[231, 249] Development of complications such as a stricture, abscess or fistula would increase the risk of surgery.[76, 230, 266] Extensive CD with ileocolitis or jejunoileitis (proximal small bowel) also increased the risk for surgery.[182, 266, 332] Presence of granulomata in two adult studies was associated with increased surgery but this was not reproduced in any paediatric cohort.[230, 232, 254, 257] A paediatric study by Kugathasan et al[319] demonstrated that the presence of 3020insC mutation in the CARD15 gene significantly increased the risk of surgery (HR: 7.78; 95% CI: 2.74-22.1), occurring earlier in the disease course.

Following surgical resection, there are several predictors for duration of disease remission. Shorter remission occurred in those who had surgery for medically resistant disease compared to strictures or perforation.[329] Earlier surgery following diagnosis was associated with a significantly prolonged remission, shown in the study by Griffiths et al[329] where children with disease duration of less than one year had a significantly longer postoperative remission. An adult study by Aratari et al[333] found that ileocaecal resection at diagnosis was associated with a significantly prolonged remission compared to later surgery.

The risk of clinical disease recurrence following resection has been reported as 17% of children at one year following initial surgery, 40% after three years and 50-60% after five years.[326, 327, 329, 330, 334, 335] The risk of subsequent surgery was 10-15% with a mean interval of six years.[149, 266, 326, 335] The use of post-operative metronidazole, aminosalicylates and azathioprine/6-mercaptopurine may protect against recurrent disease.[330, 336-338] The site of surgical resection has an impact on recurrence with small intestinal or ileocaecal CD associated with a decreased risk compared to extensive disease.[146, 329, 330, 334] In addition, children with a higher disease activity (PCDAI) at initial surgery may have a significantly greater risk of recurrence.[330]

4.9.2: Colectomy in Ulcerative Colitis

Colectomy in UC should be curative. Similar to CD, the main indication for surgical resection is medically resistant disease and/or perforation in toxic megacolon. Undertaking a proctocolectomy or a subtotal colectomy is not without problems, such as increased defaecation rates, looser bowel actions, faecal urgency with risk of incontinence and problems with cuffitis or pouchitis.

The reported rates of colectomy in paediatric UC is approximately 3-8% by the first year following diagnosis, 10% after two years, 12-15% after three years, 20% after five years and 26-40% after ten years (table 4.4).[75, 134, 183, 212, 324, 339] The cumulative colectomy rate was higher at 16.7 and 35.6% at one and three years respectively in the hospital based study from Utah (USA).[340]

There are conflicting reports of changes in colectomy rates over time. The study by Michener et al[341] demonstrated a decrease in colectomy rates from 48.9% (1955-1964) to 26.2% (1965-1974). A further study with a smaller paediatric cohort, reported a decrease in rates from

12.5% (1984-1989) to 1.2% (1990-1995).[14] In comparison, a larger study demonstrated no change in the three year resection rates in children from Ontario (Canada) diagnosed between 1994-1997 and 2001-2004 (10.9% vs 12.9%).[324] Similarly, the colectomy rate in children from Calgary (Canada) remained stable from 1983 to 2009.[342]

Children with moderate to severe disease and extensive colitis at diagnosis, and the presence of deep ulceration on colonoscopy have an increased risk for a colectomy.[134, 137, 212, 315, 317, 343-345] In addition, extension of disease over time and/or corticosteroid dependency may predispose a child to resection[134, 137, 212, 317, 343] Other predictors include the presence of extra-intestinal manifestations at diagnosis, fever and weight loss.[8, 134]

Table 4.4: Frequency of colonic resection in children with UC.

Authors	**Country**	**Year**	**1yr**	**2yrs**	**3yr**	**5yr**	**10yr**	**Overall rate (mean/median period)**
Michener et al[341]	UK	1955-1974						35.7% (11.8yrs)
Sedgwick et al [339]	UK	1983-1987				15%	26%	
Lindberg et al [14]	Sweden	1984-1995						5.3% (2.2yrs)
Gower-Rousseau et al[134]	France	1988-2002	8%	11%	15%	20%		24% (6.4yrs)
Newby et al [183]	UK	1997-2003	2.9%					17.6% (3.3yrs)
Howarth et al [212]	UK	2000-2003		9%				
Benchimol et al [324]	Canada	1994-2004			12.7%			
Moore et al [340]	USA	1997-2007	16.7%		35.6%			
Van Limbergen et al [75]	Scotland	2002-2008				26.1%	40.9%	

4.10: Nutrition and Growth

Growth is important in children and adolescents. As discussed in the previous review (chapter 3) multiple factors impact upon growth in IBD, including poor oral intake, malabsorption and increased energy requirements. Children with CD usually present with impairment in anthropometric parameters at diagnosis, compared to UC. The goal of therapy is to suppress the inflammation and optimise growth. Therefore, does growth improve in IBD following diagnosis?

4.10.1: Crohn's Disease

4.10.1.1: Changes in Weight following Diagnosis

Not surprisingly improvement in nutritional state following initiation of therapy in CD has been demonstrated in several studies. In the study by Spray et al,[206] the weight for height z-score in children with CD increased significantly from -1 to 1.1 within three months of referral and treatment. Sylvester et al[209] showed that children who had significantly lower diagnostic BMI z-scores compared to healthy children at diagnosis, underwent a significant rise in their BMI within the first year following treatment such that after two years there was no significant difference with healthy children. Other studies have also shown improvement in weight and BMI with initiation of therapy for CD.[210, 216, 325]

4.10.1.2: Changes in Height over the Disease Course

There are conflicting reports of changes in height over both the short and long-term with initiation of therapy. In the study by Griffiths et al,[217] the height z-score for the group improved by 0.35 over four years. The study by Sawczenko et al,[211] also demonstrated an improvement in height z-score of 0.21 over a mean period of ten years.

On the other hand, other studies revealed continued poor growth despite therapy.[183, 209, 210, 213, 325] In the study by Sylvester et al,[209] the height z-score had not changed over the first two years following diagnosis. In the Northern France study by Vasseur et al,[210] the height z-score of children with CD had not changed over the six year period from -0.38 at diagnosis to -0.32 at the last follow-up. In comparison, the study by Pfefferkom et al[213] on pre/early pubertal children demonstrated that within the first two years following diagnosis, the height velocity z-score increased significantly from -0.71 to 0.26 but their height z-scores had not changed with values of -0.49 at diagnosis, -0.5 at one year and -0.46 at two years. Thus, therapy for CD may improve the height velocity but this may not be enough to compensate for their initial height deficit in the setting of ongoing inflammation. In the Scottish study by Malik et al,[216] children with CD demonstrated a significant increase in the mean height velocity between the first and third year following diagnosis, but the mean height z-score remained the same. Furthermore, children who remained pre-pubertal during the study period had no increase in the height velocity or height z-scores compared to those progressing through puberty who underwent significant increases in both the height and velocity z-scores.[216] Finally, it was disappointing that the cumulative incidence of growth failure (height

or height velocity below the 5th percentile) was 9.8% after ten years of disease despite therapy.[124]

Generally, most studies have demonstrated that the final adult height is suboptimal compared to both the normal population or predicted mid-parental height.[146, 204, 211, 217, 346-348] In the study by Griffiths et al,[217] the adult height z-score was -0.82. Between 37 to 88% of children with CD will have height deficits upon reaching adulthood.[346, 347, 349] The mean final adult height was 2.4cm less than the predicted mid-parental height, and 19% of the children had an adult height which was more than 8cm less than the predicted height in a British cohort.[211] In contrast, Ferguson et al[221] from the UK demonstrated no difference in final adult height compared to the normal healthy population.

4.10.1.3: Influences on Nutrition and Growth in Crohn's Disease

Many factors impact upon growth in children. The age of onset of disease is important. CD will have a greater impact on growth in those who are pre-pubertal or in early puberty compared to those with disease onset in later puberty where most of the growth has already been attained. In addition, there are gender differences impacting upon growth. Girls enter puberty at a younger age (approximately 11 years of age) compared to boys (approximately 13 years of age), and the peak growth in girls occurs in mid-puberty prior to menarche whereas in boys it occurs later and lasts longer.[218]

4.10.1.3.1: Influence of Gender

Gender does impact weight. In a paediatric study from France, girls demonstrated a significantly greater improvement in weight z-scores compared to boys (+0.67 vs +0.23; p=0.006), but this could be influenced by the fact that they had a significantly lower weight z-score at diagnosis. On the other hand, there were no gender differences in BMI.[210]

Several studies have shown that boys have impaired growth compared to girls.[124, 210, 217, 348, 350] Following initiation of therapy, girls have a greater improvement in height as demonstrated in the study by Griffiths et al,[217] where girls who were Tanner stage 1 or 2 at diagnosis had an improvement in height z-score of 0.66 which was significantly greater than the 0.16 in boys over a mean follow-up period of four years. In the paediatric study by Vasseur et al,[210] the height z-score in girls improved significantly (+0.32) from diagnosis to maximal follow-up (median of 6 years) compared to the non-significant change in boys. In addition, the boys were significantly shorter than the girls (-0.43 vs -0.04) at maximal follow-up.[210] The

cumulative incidence of growth failure (height for age or height velocity below the fifth percentile) was significantly greater in boys compared to girls over the ten year period in a North American paediatric cohort with an incidence of 7% (vs 2.7%) and 12.6% (vs 4%) after five and ten years respectively.[124]. In one study, male children achieved an impaired adult height compared to females who had no deficits.[348]

4.10.1.3.2: Diagnostic Age

Younger children with CD may demonstrate a greater improvement in BMI compared to older children.[210] In contrast, there are conflicting reports with regard to the influence of age at diagnosis on height. In the study by Pfefferkorn et al,[213] children diagnosed at nine years or older demonstrated suboptimal height velocity within the first two years following diagnosis compared to those less than nine years of age who had significantly greater mean height velocity. On the other hand, a French study demonstrated that younger children were at risk of having pronounced growth failure following diagnosis.[210]

4.10.1.3.3: Impact of the Diagnostic Weight and Height Parameters on Subsequent Growth

Weight, BMI and height at diagnosis may be strongly associated with subsequent changes in anthropometrics following diagnosis. Children diagnosed with poorer parameters may continue to have significant deficits over the disease course.[210] In a British paediatric cohort, children diagnosed with minimal height deficits were likely to attain better adult height.[211]

4.10.1.3.4: Other Factors

Greater disease severity may hinder improvements in weight and height.[213, 214, 217, 351] In the study by Wine et al,[214] it was demonstrated that hospitalisation for two or more weeks in the year prior to the lowest growth measure increased the risk of weight failure (z-score < 2) during follow-up. Both isolated small bowel disease, especially jejunal involvement, and diffuse CD has been associated with impaired growth and suboptimal final adult height.[211, 213, 352] A low albumin was associated with decreased BMI z-scores on linear regression analysis of a mixed effect model in a Scottish study by Malik et al.[216] The presence of extra-intestinal manifestations at diagnosis has been shown in one study to be associated with shorter height at follow-up after six years.[210]

4.10.1.3.5: Impact of Therapy

Medications for IBD have been assessed with regard to the impact on growth. Enteral nutrition and infliximab have been associated with improvements in both weight/BMI and height within the first two years following diagnosis, especially in pre/early pubertal children.[219, 353-367] In a study by Turner et al[360] where methotrexate was introduced in children who were resistant or intolerant of thiopurines, their height velocity z-score improved from -1.9 to -0.14 within twelve months. In a Scottish study by Malik et al,[216] the use of prednisolone, azathioprine and methotrexate had a negative association with subsequent height z-scores, which may be related to the fact that children treated with these medications probably had a more severe disease process. In another study by the same group, the use of enteral nutrition had no impact upon height at two years, but the population included children at various stages of puberty.[368] Adalimumab may have a positive impact upon height improvement after six months of therapy, but further research is needed.[369]

Surgical resection in children with medically resistant disease and/or complications may improve their nutritional state and growth.[146, 216, 217, 219, 329, 330, 334, 347, 352, 370-373] Again, the positive impact is greater in pre-pubertal children.[219, 335, 347, 370, 373] Following surgical resection, growth may remain suboptimal if there is residual disease and/or subsequent clinical recurrence, especially if occurring within a short period of time after surgery.[352, 370] Overall, there is no significant difference in final adult height between children treated with medical therapy or surgical resection.[146, 217]

4.10.2: Ulcerative Colitis

UC has less impact on weight and height, which is related to the fact that it is a mucosal disease and usually not involving the small intestine. Children with UC are less likely to have growth issues following diagnosis and, usually attain normal adult height.[204, 221, 348, 349] The presence of poor weight, BMI and/or height in a child with UC should prompt reassessment for the possibility of CD.[17]

4.11: Future Risk of Cancer

4.11.1: Ulcerative Colitis

There are conflicting reports on the risk of colorectal cancer in UC. Older studies undertaken at tertiary centres of patients with more severe disease have shown significantly increased risk of colorectal cancer. In comparison, some population based studies have reported no

increased risk of colorectal cancer compared to the background population whereas others have reported an increased risk.[374-378] In the meta-analysis by Eaden et al,[376] the overall prevalence of colorectal cancer was 3.7% with an overall incidence of 1 in 300 per year. Recent population based studies have shown incidence figures that were as low as 1 in 1600 per year.[374, 378-380] The risk of colorectal cancer may be greater in those with increased duration of disease, more extensive involvement of the colon and, in children and young adults independent of duration.[376, 381-388] Several studies have demonstrated that a positive family history of colorectal cancer was associated with a greater risk of malignancy in UC.[389-391] The impact of primary sclerosing cholangitis on the risk of colorectal cancer has generated mixed results with some studies demonstrating increased risk, whilst others reported no greater risk.[392-400] Hopefully, the future risk of colorectal cancer in UC may improve with closer endoscopic surveillance of the colon and the potential protective effect of aminosalicylates (UC) and ursodeoxycholic acid (UC/PSC).[391, 401-406]

4.11.2: Crohn's Disease

Like UC, there is an increased risk of colorectal and small bowel cancer reported in CD.[407-412] The question of extra-intestinal cancers has generated mixed results. Some studies have shown a significant association with leukaemia, lymphoma and tumours of connective tissue, skin, liver, biliary tract, uterus, urinary bladder, brain or lung.[374, 388, 413-417] A meta-analysis by Pedersen et al,[416] demonstrated that patients with CD had an increased risk of upper gastrointestinal, lung, urinary bladder and skin cancers and those with UC had a significantly increased risk of leukaemia, liver and biliary cancer, but a decreased risk of pulmonary cancer.

4.12: Mortality

There are several issues limiting the interpretation of data from studies on mortality in IBD. Hospital based studies reported a higher mortality rate than population based studies given their sicker cohort. Reported deaths in childhood onset IBD are limited by the smaller cohort compared to adults, and the restricted follow-up period. In earlier Danish and Italian studies where the follow-up was 8-10years, no significant increase in mortality was demonstrated, however in subsequent studies on the same cohort after 15-17 years, there was a significant increase in standardised mortality ratio (SMR) of 1.3 and 1.5 respectively.[418-421] It is worth commenting on the difficulty in interpreting mortality rates in older studies given the changes in approach to medical therapy and timing of surgery.

Death in IBD may occur as a result of nutritional or metabolic complications of disease, infection, perforation of the bowel, adverse effects of medications both in the short and long-term, surgical complications and malignancy. Lastly and more importantly, the psychological impact of IBD may contribute to depression and possible suicide.[182, 184, 421-431]

4.12.1: Crohn's Disease

Paediatric CD studies have reported a mortality frequency from less than 1% to 9% over a mean period of seven to nine years.[129, 146, 147, 182, 266] Several studies have not shown an increased mortality with SMR of 0.72 to 1.2.[432-436] On the other hand, studies from Sweden, Denmark, Italy, England and the European Community IBD study (EC-IBD) have shown significantly increased SMR with values of 1.3 to 1.85 over a mean period of 10-17 years.[375, 418, 419, 437-439] There are two time periods of increased mortality following diagnosis which includes the first five years and then either after 13 years in one study or 21-25 years in another study.[419, 420, 433, 434, 436, 438, 440]

Frequency of mortality due to the disease itself or its complications ranged between 16 and 40% of all deaths and occurred within 3-8 years following diagnosis.[136, 419, 420, 432, 437, 441] Deaths due to cancer and other aetiologies unrelated to CD usually occurred later, such as non-malignant gastrointestinal diseases, hepatic disease, cancers (gastrointestinal, respiratory), lung disease, infections and genitourinary disease.[375, 418, 419, 421, 432, 437, 438, 442] There are conflicting reports on the impact of age, gender and anatomical involvement on mortality.

4.12.2: Ulcerative Colitis

Among the paediatric UC studies the reported frequency of death was 1-5% of the cohort over a mean follow-up period of 5-20 years.[8, 129, 134, 137, 184, 341, 443] Earlier studies demonstrated a higher mortality related to disease and surgical complications.[311, 382] In a paediatric study by Langholz et al,[8] the reported SMR was 5.3 over a median follow-up of eight years. In reviewing adult studies with the inclusion of paediatric onset UC, there was no increase in the overall mortality.[136, 375, 377, 424, 432, 433, 435, 438, 444-447] In the meta-analysis of population based cohort studies by Jess et al,[448] the SMR varied between 0.7-1.4 among the various studies with an overall non-significant pooled SMR of 1.1. The mortality risk was greater in the first 1-5 years following diagnosis.[377, 424, 433, 435, 438, 448] Up to a quarter of deaths were UC-

related.[136, 377, 424, 432, 446, 448] These UC-related deaths were grouped in the meta-analysis into colorectal cancer with a mean frequency of 37%, surgical or post-operative complications with a mean frequency of 44% and the remainder related to severe disease activity.[448] Other non UC reasons for death may include other gastrointestinal diseases, non-alcoholic fatty liver disease, pulmonary embolism and other respiratory illnesses.[418, 432, 438, 448] The only phenotypic feature of UC related to significantly increased mortality was the proximal extent of disease beyond the splenic flexure.[377, 382, 448]

4.13: Conclusion

Children with IBD need to be monitored closely with the aim of disease control, both with resolution of clinical symptoms and mucosal healing. There are many clinical parameters that need to be reviewed on a regular basis, contributing to the complexity of this disease. Within this review, several other aspects of disease course were not discussed, such as pubertal developmental, bone growth, psychological well-being, highest education achieved, future employment status, social relationships and fertility, which are equally important. Ideally the goal of therapy should be to optimise health and prevent irreversible complications.

Chapter 5: Description of Disease Phenotype in Australian Children Diagnosed with Inflammatory Bowel Disease

5.1: Introduction

Inflammatory bowel disease is a complex heterogeneous disorder with a variable clinical presentation. In studying this condition it is important that thorough data is collected over time, so that important information can be extrapolated and trends in disease incidence and manifestation over time and among regions can be made. The following chapters will describe phenotypic features of Australian children diagnosed with IBD.

5.2: Aims and Hypothesis

5.2.1: Aims

- Review the phenotype at diagnosis of Australian children with IBD, in comparison to already published information from other parts of the world.
- Investigate any regional variation in epidemiology and phenotype across Australia and within South Australia.
- Examine any gender and age related differences in disease phenotype.
- Describe extra-intestinal manifestations and anthropometric parameters at diagnosis.
- Describe in detail orofacial and perianal lesions in children with CD.

5.2.2: Hypothesis

- Phenotypic features of Australian children diagnosed with IBD will be similar to that previously reported in international studies.
- Age and gender related changes in disease subtype and disease distribution will be identified.
- Novel associations among the phenotypic features at diagnosis will be found.

5.3: Methodology

5.3.1: Australian Paediatric and Adolescent Inflammatory Bowel Disease Database (APAIBD)

The Australian Paediatric and Adolescent Inflammatory Bowel Disease Database (APAIBD) was established in 1996 with the aim of collecting demographic, clinical, anthropometric and laboratory data at time of diagnosis in children with established and newly diagnosed IBD less than 18 years of age. It is a national database to which health care professionals submit

de-identified information. The database is managed and coordinated by Dr David Moore (Gastroenterology Department of the Women's and Children's Hospital, Children, Youth and Women's Health Service, Adelaide, South Australia) with support from the Australian Paediatric and Adolescent IBD Study Group who provide the data. The database platform used is Epi Info 6.04d (January, 2001; Centers for Disease Control and Prevention, Atlanta, USA), an epidemiological program into which voluntary questionnaire based data is stored and can be analysed using the incorporated statistical package or exported in varying formats to be analysed by a range of statistical software packages. Ethical approval for the collection of this de-identified information has been obtained in all hospitals across Australia in which children with IBD are managed.

A copy of the questionnaire is found in Appendix B. Key data collected includes basic demographic data, including date of birth, gender, postcode of residence, name of health care professional and hospital involved in the child's care, ethnic and racial background, diagnosis, date of diagnosis and duration of symptoms prior to diagnosis. Importantly, the reporting doctor needs to assign the disease subtype as either CD, UC or IBDU. Guidelines on the differentiation between these disease subtypes are provided in the questionnaire.

The diagnosis of CD is established when one of the following criteria is present:

1. Symptoms of diarrhoea and/or abdominal pain and/or fever with medical imaging features of small bowel disease typical of CD.
2. Symptomatic mucosal lesion of any portion of the gastrointestinal tract (including microscopic lesions from lips to perianal skin) demonstrated by endoscopy, histology which shows features typical of CD and/or non-caseating granulomata (more than one).
3. Terminal ileal inflammatory lesion demonstrated at operation for acute abdominal pain with typical gross and histological appearance of CD and subsequently leading to chronic symptoms consistent with CD.

Exclusion criteria include symptoms of less than three months with acute inflammatory ileitis or colitis due to infectious cause proven by stool examination, serology or culture, and /or other disease processes which may mimic CD, such as tumours and appendiceal abscesses.

UC is diagnosed when there are symptoms of haematochezia and/or diarrhoea with rectal or colonic histology consistent with UC and the presence of continuous mucosal disease

involving the rectum and/or extending proximally in the colon as assessed by endoscopy, histology and/or medical imaging. Infectious colitis needs to be ruled out by at least one negative stool microscopy and culture.

IBDU is established when there are symptoms consistent with either CD or UC, with histological and endoscopic evaluation consistent with IBD, but not definitive for either CD or UC.

The extent of gastrointestinal disease is recorded with the presence of granulomata and/or prominence of eosinophils. In addition, the severity of the colitis is rated as per the provided guideline:

1. Normal endoscopic mucosa but has microscopic inflammation.

1a. Loss of vascular pattern and/or increased friability and/or erythema on endoscopic evaluation but no microscopic inflammation.

2. Loss of vascular pattern and/or increased friability and/or erythema and/or aphthous ulcers with microscopic inflammation.
3. Granular mucosa and/or exudates and/or pus
4. Discrete areas of ulceration and/or cobblestoning.
5. Confluent ulceration and/or pseudopolyps
6. Toxic dilatation.

The presence and nature of perianal disease, the presence and site of fistulous and/or stricturing disease, extra-intestinal manifestations and other coexisting conditions are recorded.

The country of birth for the child, parental racial and ethnic origin, first degree family history of IBD and the child's exposure to cigarette smoking is also included. Anthropometric data, pubertal stage and the onset of menarche is recorded. Epi Info is used to calculate the weight and height percentile and z-scores as per CDC/WHO (World Health Organisation) 1978 growth charts.[449]

Laboratory results at diagnosis that are recorded in the database include haemoglobin (Hb), packed cell volume/haematocrit (PCV/Hct), platelet count, erythrocyte sedimentation count (ESR), white cell count (WCC), c-reactive protein (CRP), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), perinuclear

antineutrophil cytoplasmic antibody (p-ANCA) and anti-*saccharomyces cerevisiae* antibodies (ASCA IgA and IgG). ASCA IgA and IgG are considered positive when the value is greater than 25 units/ml (Central Sydney Laboratory Service, Royal Prince Alfred Hospital, Sydney, NSW, Australia).

Health care professionals submit the details by completing the hard copy of the questionnaire (Appendix B) and either sending it by post or fax, e-questionnaire for email response or web based (http://www.wch.sa.gov.au/services/az/divisions/paedm/gastro/files/gastro-database.html). An email is sent on a monthly basis to all health care professionals in Australia managing children as a reminder of any new IBD cases. In addition, the Australian Crohn's and Colitis Association may send contact details of any children with IBD following parental permission and then the managing doctor will be contacted to provide further details. Any missing or extreme data prompted a letter or email to the reporting clinician to clarify the information.

5.3.2: Missing Incident Cases of IBD in South Australia

The Women's and Children's Hospital electronic database of discharges was used to identify every child diagnosed with CD, UC or colitis since 1996. Furthermore, the case notes of Dr Paul Hammond, a paediatric gastroenterologist who is the sole practitioner who practices part-time outside of the Women's and Children's Hospital, including endoscopic evaluation in a private hospital, was reviewed. Any child identified and not in the APAIBD database, had their information collected. Data collection in South Australia was thought to be complete in children aged less than 16 years

5.3.3: Statistical Analysis

The Epi Info database was updated from version 6.04d to the current version 3.5.1 (August 2008). Nutritional data were updated with new percentiles and z-scores using values published by the Centers for Disease Control and Prevention, Atlanta, USA (CDC 2000).[450] Body mass index (BMI) and the associated percentile and z-score were calculated by the nutritional program in Epi Info. Weight and growth (height) failure were defined as z-scores less than -2. The Montreal classification for CD and UC disease extent and CD behaviour was applied.[18] Data collection and analysis was undertaken prior to the publication of the Paris modifications.[121]

Statistical testing was done within Epi Info 3.5.1. Groups of interest were compared using independent t-tests for two group comparisons and ANOVA for more than two groups when data were normally distributed. Many of the continuous measures were not normally distributed and could not be transformed to normality, so non-parametric testing was undertaken. Comparison between two groups was undertaken by Mann-Whitney, and Kruskal-Wallis testing for more than two groups. Results were presented as medians with inter-quartile range (IQR). Categorical comparison was made by chi-square analysis with results reported as corrected chi-squares (Yates). Fisher's Exact Test was used when the expected cell values were less than 5 in one or more cells. Confounders were investigated by means of stratification and regression modelling. All p-values were reported as two-tailed and the significance level for rejecting null hypotheses was taken to be 0.05.

The database was interrogated with regard to the phenotypic features at diagnosis. Age and gender related differences in disease presentation was analysed. The diagnostic age was divided into periods of six years, so that differences in phenotype between the young (less than six years) and older children can be undertaken.[68, 69, 130] Potential associations between various diagnostic features were searched, any positive relationship was further analysed according to potential confounders. Further analysis concentrated on specific phenotypic features, such as orofacial and perianal CD, extra-intestinal manifestations, anthropometric details and then comparisons between states were undertaken.

5.3.4: South Australian Incidence Figures

Children who were aged less than 16 years of age and diagnosed with IBD within South Australia between 1996 and 2009 were extrapolated. The post-code was utilised to categorise their residence at the time of diagnosis according to the statistical division and subdivision from the Australian Bureau of Statistics.[451] If their post-code was found in two or more statistical divisions then the hospital electronic database and/or case-notes were reviewed to identify their exact residential division/subdivision.

The population figures of children in South Australia and within each statistical division according to the Australian Bureau of Statistics consensus in 1996, 2001 and 2006 was utilised.[451] Linear (straight-line) interpolation was then calculated to estimate the population between the censuses, and figures for 2007 to 2009 was assumed to be the same as 2006.

Incidence figures per 100,000 person years were calculated for IBD, CD, UC and IBDU. Statistical comparison between different divisions and trends over time was determined.

5.3.5: Ethics Approval

Analysis of APAIBD, review of the Women's and Children's Hospital electronic database for discharge diagnosis and subsequent case notes review was approved by the ethics board of the hospital.

Chapter 5.4: Analysis of the National Database

5.4.1: APAIBD Database

Following its establishment in 1996 till June 2010, 2101 children diagnosed with IBD prior to their 18th birthday have been recorded in APAIBD. Most of these children were recorded prospectively but some diagnosed prior to 1996 were also entered. The details of these children are provided in table 5.4.1. The median age at diagnosis was 11.8 years (IQR: 9, 13.9) with a male predominance (56.5%). Most of these children were either pre-pubertal or in early puberty (Tanner stage 1-2). The predominant diagnosis was CD with a frequency of 59.4% followed by UC (30%). The majority of the children were Caucasian with 0.3% being of Australian Indigenous race. Diagnostic upper gastrointestinal endoscopy was undertaken in 89.1% and colonoscopy in 98.4% of children. The phenotypic features at diagnosis among the disease subtypes of CD, UC and IBDU are presented in table 5.4.2.

Table 5.4.1: Details of the children with IBD at time of diagnosis (n=2101).

	Details of Children
Age at diagnosis (IQR)	11.8 years (9, 13.9)
Duration of symptoms prior to diagnosis (IQR)	20 weeks (8, 52)
Gender distribution (males)	56.5%
Disease subtype	
CD	1247 (59.4%)
UC	631 (30%)
IBDU	223 (10.6%)
EIMs	719 (35.3%)
First degree family history of IBD	189 (9.6%)
Caucasian racial origin	1917 (95.9%)
Tanner stage:	
1	896 (64.3%)
2	117 (8.4%)
3	109 (7.8%)
4	129 (9.3%)
5	142 (10.2%)
Weight z-score (IQR)	-0.36 (-1.24, 0.4)
Height z-score (IQR)	-0.19 (-0.91, 0.6)
BMI z-score (IQR)	-0.42 (-1.37, 0.36)

5.4.2: Age Related Differences in Disease Subtype

Median age at diagnosis was significantly older in children with CD compared to UC and IBDU (table 5.4.2). Comparison of disease subtype with age revealed that there was significantly greater proportion of UC and IBDU in those diagnosed less than six years of age compared to older children in whom CD predominated ($p < 0.0001$) as shown in figure 5.4.1

and 5.4.2. On linear regression modelling, the proportion of children with CD increased significantly and UC/IBDU decreased with increasing diagnostic age (p<0.0001).

Table 5.4.2: Comparison of phenotypic presentation of children with CD, UC, and IBDU.

	CD	UC	IBDU
Age at diagnosis (IQR)	12.2yrs[a,b] (9.6, 14.2)	11.4yrs[a] (7.3, 13.6)	10.7yrs[b] (7.1, 13.3)
Duration of symptoms prior to diagnosis (IQR)	24wks[a] (10, 52)	13wks[a] (6, 30)	18.5wks (8, 43)
Gender (males)	58.8%[a]	52.8%[a]	54.7%
EIMs	41.2%[a,b]	26.3%[a]	27.5%[b,]
First degree family history of IBD	10%	8.2%	10.7%
Wt z-score (IQR)	-0.58[a,b] (-1.48, 0.21)	-0.09[a] (-0.82, 0.6)	0.02[b] (-0.81, 0.73)
Ht z-score (IQR)	-0.33[a,b] (-1.11, 0.41)	-0.02[a] (-0.68, 0.74)	0.1[b] (-0.67, 0.79)
BMI z-score (IQR)	-0.62[a,b] (-1.55, 0.18)	-0.16[a] (-0.95, 0.5)	-0.04[b] (-0.89, 0.58)

[a]significance of p<0.05 between CD and UC.
[b]significance of p<0.05 between CD and IBDU.

Figure 5.4.1: Year of age at diagnosis among the various disease subtypes (n=2101).

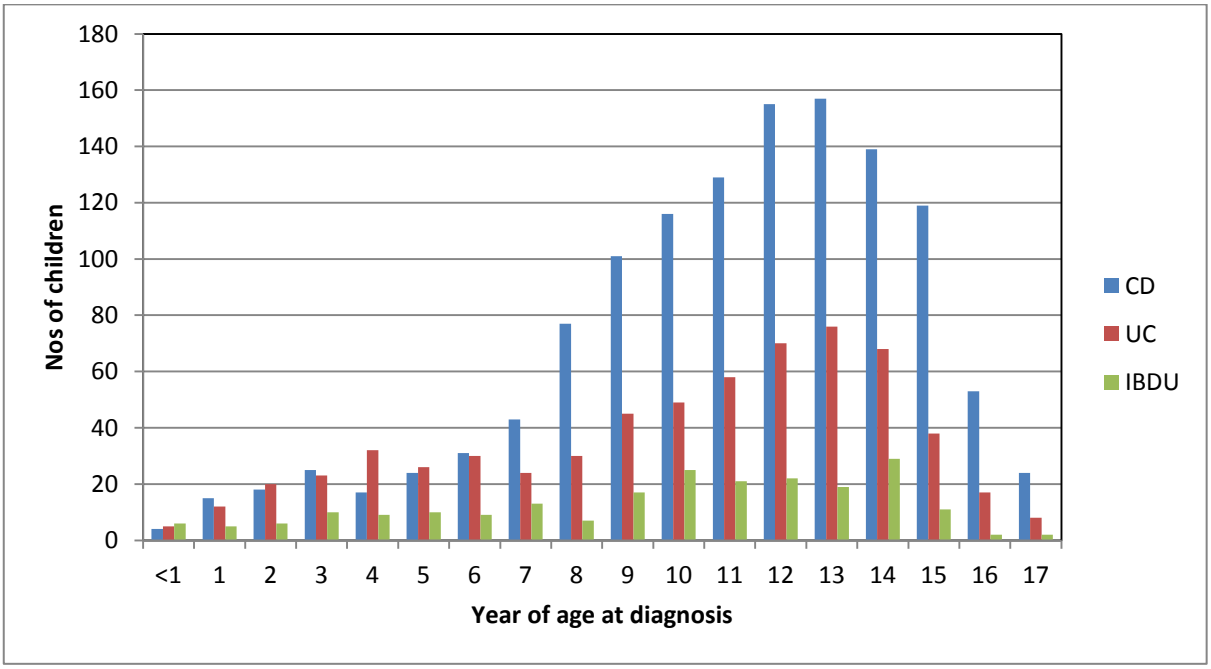
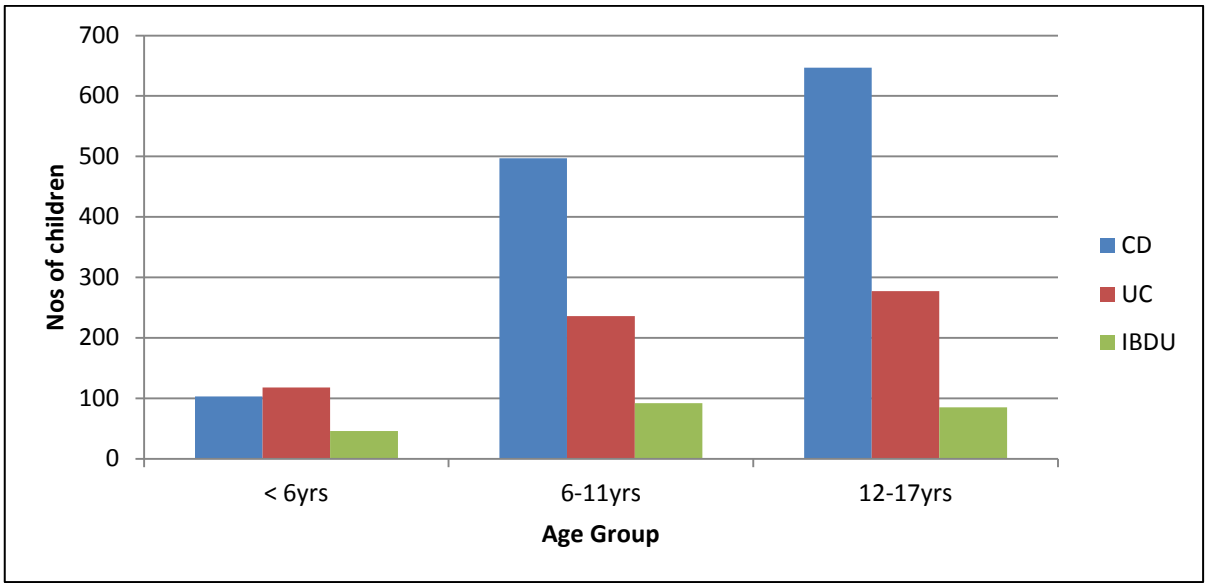


Figure 5.4.2: Disease subtypes among the age groups.



5.4.3: Gender

There was a significant male predominance in children aged less than 18 years diagnosed with IBD compared to the background age matched Australian paediatric population (56.4% vs 51.3%; one sample Z-test: 4.95; p <0.05).[451] When stratified according to disease subtype, this male predominance was found only among those with CD (58.6% vs 51.3% of Australian children; one sample Z-test: 5.3; p <0.05) and not in those diagnosed with UC or IBDU. Thus, the male predominance was greater in CD compared to UC (table 5.4.2), with an even greater difference in those aged less than six years (68.9% vs 50.8%; p 0.01).

5.4.4: Crohn's Disease

5.4.4.1: Anatomical Extent of Disease

According to the Montreal classification, 117 (10.1%) children presented with isolated terminal ileum disease (L1), 382 (32.9%) with isolated colonic disease (L2) and 662 (57%) with combined ileocolonic disease (L3). The frequency of lower gastrointestinal disease involvement is shown in table 5.4.3. There were 816 children out of 1034 (78.9%) with upper gastrointestinal involvement (L4), of which 778 children had concurrent lower gastrointestinal involvement. Presence of L4 was significantly associated with ileocolonic CD (L3; 85.1%) compared to isolated terminal ileum (L1; 74.2%; p 0.013) and isolated colonic disease (L2; 71.2%; p <0.0001). Orofacial manifestation was present in 8.9% and

perianal disease in 46% of children at diagnosis. Both orofacial and perianal CD will be discussed in the following chapters.

5.4.4.2: Influence of Age and Gender on Disease Extent

The age distribution in CD revealed that half (51.9%) were aged between 12 and 17yrs at diagnosis compared to 8.3% in those less than 6yrs and 39.9% in 6-11yrs age group. The male predominance was significantly greater (68.9%) in those less than 6 years of age compared to older children (6-17 years of age; 57.9%; p 0.037).

There were significant differences in lower gastrointestinal disease distribution with age at time of diagnosis (table 5.4.3; figure 5.4.3). In children less than 6 years of age at diagnosis, 50% presented with isolated colonic disease compared to 34.1% in the 6-12 year age group and 29.4% of those aged 12-17 years. Logistic regression for lower gastrointestinal involvement with several independent predictors (gender, diagnostic delay, disease behaviour), revealed a significantly decreasing frequency of isolated colonic (L2) with increasing age (OR 0.26; 95% CI: 0.14, 0.51; p=0.0001) and a significantly increasing frequency of isolated terminal ileum (L1; OR 9.3; 95% CI: 1.9, 46.5; p=0.007) and ileocolonic involvement (L3; OR 2.1; 95% CI: 1.1, 3.9; p=0.022). There were no significant age related differences in upper gastrointestinal disease (L4).

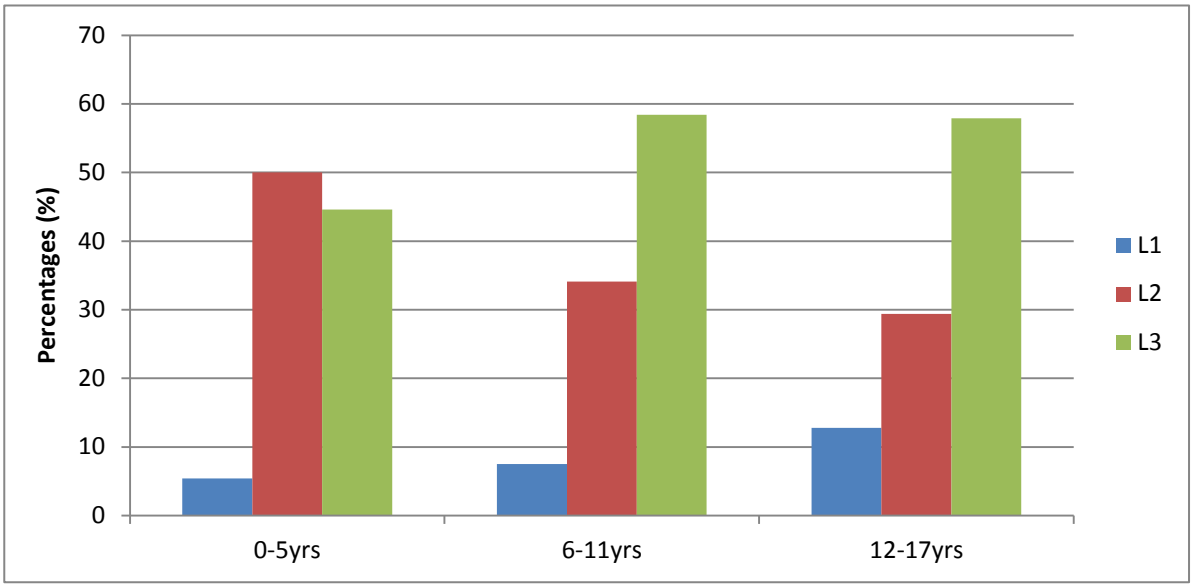
Children with colonic involvement (L2 or L3) presented with a shorter duration of symptoms compared to those with isolated terminal ileum disease (table 5.4.3).

Table 5.4.3: Characteristics of the children according to lower gastrointestinal disease distribution.

	Isolated terminal ileum disease (L1)	**Isolated colonic disease (L2)**	**Ileocolonic disease (L3)**	**Entire CD cohort**
Number of children	117 (10.1%)	382 (32.9%)	662 (57%)	1161
Age at diagnosis (IQR)	13.1yrs[a, b] (10.7, 15.1)	11.7yrs[a,c] (9, 13.7)	12.3yrs[b,c] (9.8, 14.3)	12.2yrs (9.6, 14.2)
Gender (males)	56.4%	55.2%	60.1%	58.1%
Duration of symptoms prior to diagnosis (IQR)	31 wks[d,e] (12, 78)	24 wks[d] (9, 52)	24 wks[e] (10, 52)	24 wks (10, 52)
1st degree family history of IBD	10%	7.9%	11.1%	9.9%
EIMs	33.6%[f]	37%[g]	45.3%[f,g]	41.4%

[a]p=0<0.00001; [b]p=0.0034; [c]p=0.001; [d]p=0.0007; [e]p=0.0038; [f]p=0.025; [g]p=0.011

Figure 5.4.3: Disease distribution within each 6 year age range.



Chi square: 22.8, df=4, p=0.0001

5.4.4.3: CD Behaviour at Diagnosis

Majority of children with CD presented with inflammatory behaviour (B1) with a frequency of 92.6% followed by 5.9% with stricturing behaviour (B2) and 1.5% with penetrating behaviour (B3). There was a greater frequency of inflammatory behaviour (B1) diagnosed in those less than 6 years of age (98%) compared to older children (92.1%; p=0.05; table 5.4.4), but when analysed according to the 6 year age division (0-5, 6-11, 12-17) there were no significant differences.

Inflammatory behaviour (B1) was significantly associated with isolated colonic disease (L2; OR: 1.9; 95% CI: 1.1, 3.2; p=0.026) on multi-logistic regression. This association was negatively confounded by the presence of perianal disease, since perianal lesions were inversely associated with both the presence of inflammatory behaviour (OR: 0.55; 95% CI: 0.35, 0.85; p=0.0104) and isolated colonic disease (OR: 0.6; 95% CI: 0.46, 0.77; p <0.0001). Thus, there were no significant association between inflammatory behaviour and isolated colonic disease in the presence of perianal disease, but in its absence the positive association was present (OR: 5, 95% CI: 1.9, 16.8; p=0.002). There was a significant association between terminal ileal disease (L1 or L3) and stricturing behaviour (B2; OR: 2.6; 95% CI: 1.3, 5.4; p=0.0078) which remained significant even when other anatomical sites of disease involvement were controlled for in a logistic regression model.

Table 5.4.4: Disease behaviour at diagnosis according to age.

Age at diagnosis	0-5years	6-11years	12-17 years	Total
Inflammatory behaviour (B1)	98 (98%)	450 (92.2%)	575 (92%)	1123 (92.6%)
Stricturing behaviour (B2)	2 (2%)	31 (6.4%)	39 (6.2%)	72 (5.9%)
Penetrating behaviour (B3)	0	7 (1.4%)	11 (1.8%)	18 (1.5%)
Total	100	488	625	1213

5.4.4.4: Presence of Granulomata

Granulomata at any biopsy site were present in 19.1% (172/899) of children with CD at diagnosis. Granulomata were present in various anatomical sites of the gastrointestinal tract but the frequency of detection was greatest in biopsies from orofacial lesions (48.3%) and perianal disease (24.7%), with frequency of between 16-21% in other parts of the bowel. More males (22.8%; 122/536) were found to have granulomata on their biopsies compared to females (13.8%; 50/363; corrected chi-square: 10.7; p=0.001). On multiple regression modelling, the significant factors associated with the presence of granulomata were being male (OR: 1.63; 95% CI: 1.1, 2.4; p=0.014), presence of orofacial disease (OR: 4.3; 95% CI: 2.6, 7.2; p <0.0001), the presence of perianal disease (OR 1.8; 95% CI: 1.2, 2.6; p=0.003) and inflammatory CD behaviour (B1; OR: 2.9; 95% CI: 1.1, 7.7; p=0.03). The presence of stricturing behaviour (B2) was significantly associated with decreased frequency of granuloma detection (OR: 0.3; 95% CI: 0.1, 0.9; p=0.032).

5.4.4.5: Serological Markers in CD

5.4.4.5.1: ASCA IgA/IgG Positivity

Anti-*Saccharomyces cerevisiae* antibody (ASCA) was reported in 161 children with CD (12.9% of CD cohort). ASCA IgA was positive in 47.8% (77/161) and IgG was positive in 49.7% (80/161). Children who were ASCA IgA or ASCA IgG positive were significantly older than the rest of the cohort (table 5.4.5). Both ASCA IgA and IgG presence was significantly associated with disease involvement of the terminal ileum (L1 or L3; ASCA IgA: p=0.0005; ASCA IgG: p=0.00006) and upper gastrointestinal tract (L4; ASCA IgA: p=0.003; ASCA IgG: p=0.0002). When analysing the segments of the upper gastrointestinal tract (L4) in a regression model, ileum (excluding terminal ileum) was significantly associated with positive ASCA IgA (OR: 3.52; 95% CI: 1.14, 10.83; p=0.028) and positive ASCA IgG (OR: 3.06; 95% CI: 1.00, 9.42; p=0.05). On logistic regression modelling,

terminal ileal disease and upper gastrointestinal disease remained significantly associated with positive ASCA IgA and IgG.

Table 5.4.5: Comparison of disease phenotype of children with CD who were ASCA IgA and/or IgG positive.

	ASCA IgA +ve (n=77)	**ASCA IgA -ve (n=84)**	**p-value**	**ASCA IgG +ve (n=80)**	**ASCA IgG -ve (n=81)**	**p-value**
Age at diagnosis (IQR)	12.9yrs (10.2, 14.8)	11.4yrs (9.4, 13.8)	**0.034**	12.8yrs[c] (10.4, 14.7)	11.4yrs[c] (9.3, 13.7)	**0.02**
Gender (male)	57 (74%)	60 (71.4%)	0.85	57 (71.3%)	60 (74.1%)	0.82
Duration of disease prior to diagnosis (IQR)	26wks (12, 52)	22wks (11, 52)	0.27	26wks (12, 52)	22wks (10, 52)	0.36
1st degree family history of IBD	7 (9.2%)	8 (9.6%)	0.86	5 (6.3%)	10 (12.5%)	0.29
EIMs	32 (42.1%)	43 (51.8%)	0.29	39 (48.8%)	36 (45.6%)	0.81
Disease distribution						
Orofacial disease present	8 (10.5%)	16 (19%)	0.2	10 (12.7%)	14 (17.3%)	0.55
Any terminal ileum disease (L1/L3)	67[a] (88%)	49[a] (62.8%)	**0.0005**	70[d] (89.7%)	46[d] (60.5%)	**0.00006**
Upper GIT disease (L4)	64[b] (85.3%)	53[b] (63.1%)	**0.003**	69[e] (87.3%)	48[e] (60%)	**0.0002**
Perianal disease present	44 (58.7%)	45 (54.2%)	0.69	51 (64.6%)	38 (48.1%)	0.054
Disease behaviour						
Stricturing/penetrating disease behaviour (B2/B3)	8 (10.4%)	7 (8.3%)	0.86	8 (10%)	7 (8.6%)	0.98
Lab parameters						
ESR (mm/hr; IQR)	41 (23, 62)	27 (15, 50)	**0.01**	36 (19, 62)	30 (18, 52)	0.3
Albumin (g/L; IQR)	31 (26, 36)	35 (30, 40)	**0.008**	31 (26, 37)	35 (31, 40)	**0.002**

Regression modelling: [a]p=0.003; [b]p=0.03; [c]p=0.05; [d]p=0.0005; [e]p=0.002.

5.4.4.5.2: p-ANCA Positivity

Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) was recorded in 343 children with CD (27.5% of cohort), of which 66 (19.2%) were positive. The presence of p-ANCA was significantly associated with isolated colonic CD (L2; OR: 3; 95% CI: 1.7, 5.3; p=0.0002) and significantly less frequency of perianal disease (OR: 0.36; 95% CI: 0.19, 0.69; p=0.002), even when controlling for age, gender, upper gastrointestinal disease and behaviour. Having a positive family history of IBD in first degree relatives was associated

with increased frequency of p-ANCA positivity (35.5% versus 17.9% in those with no family history; corrected chi-square 4.51; p=0.034). This association continued to be present when diagnostic age, gender, Montreal disease location and behaviour, orofacial, perianal disease were included in logistic regression model (OR: 2.64; 95% CI: 1.1, 6.3; p=0.03).

5.4.5: Ulcerative Colitis

5.4.5.1: Age and Gender related differences in Disease Distribution

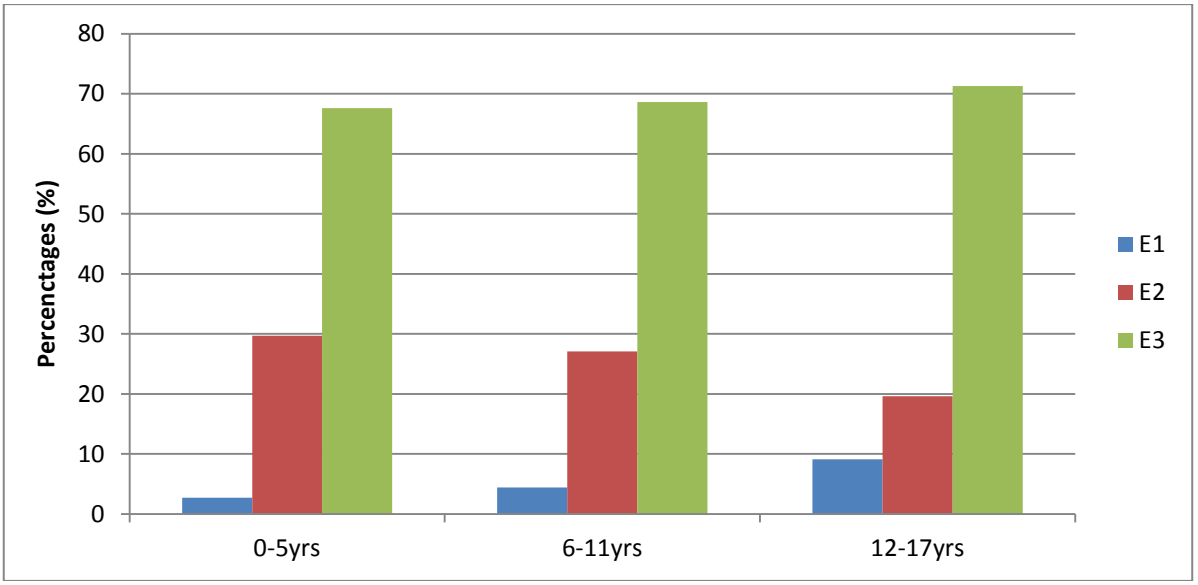
Details on the distribution of disease in UC were available on 605 children, with 421 having extensive colitis (E3), 147 with left sided colitis (E2) and 37 children with disease limited to their rectum (E1). Details of these children are presented in table 5.4.6. Of those children with extensive colitis, the majority had pancolitis (79.9%; 330/413). There was a significant difference in the median age at diagnosis among the children with differing disease extent (table 5.4.6). Children with proctitis (E1) were older than the others. When analysed according to the 6 year age groups (figure 5.4.4), there was an increase in isolated proctitis from 2.7% in those less than 6 years of age to 9.1% in those aged 11-17 years (Chi square: 7.46, df=2, p=0.02). With increasing age at diagnosis, there was a significant increase in the frequency of proctitis (E1; OR: 10.2; 95% CI: 1.3, 81.2; p 0.0286) and a decrease in left sided colitis (E2; OR: 0.39; 95% CI: 0.2, 0.76; p 0.0055) whilst the frequency of extensive colitis (E3) remained static on linear regression modelling. Gender had no significant influence on the disease distribution (table 5.4.6).

Table 5.4.6: Characteristics of children with UC (n=605).

	Proctitis (E1)	**Left sided colitis (E2)**	**Extensive colitis (E3)**	**Total UC cohort**
Nos of children	37 (6.1%)	147 (24.3%)	421 (69.6%)	605
Age at diagnosis (IQR)	13 yrs[a,b] (11.1, 14.7)	10.8 yrs[a,c] (6.1, 13.1)	11.5 yrs[b,c] (7.6, 13.9)	11.4yrs (7.3, 13.6)
Gender (males)	56.8%	56.5%	51.5%	52.8%
Duration of symptoms prior to diagnosis (IQR)	15 wks (8, 32)	12 wks (6, 26)	13 wks (6, 30)	13 wks (6, 30)
Family history of IBD (1st degree)	2 (5.4%)	11 (8%)	34 (8.6%)	47 (8.3%)
EIMs	6 (16.2%)	32 (21.9%)	121 (28.9%)	159 (26.3%)

[a]p=0.002; [b]p=0.018; [c]p=0.007

Figure 5.4.4: Disease extent in UC at diagnosis according to age.



Chi square: 11.7, df=4, p=0.02

5.4.5.2: Other Gastrointestinal Disease Involvement in UC

Gastrointestinal disease involvement beyond the colon included the oesophagus (2.6%; 15/571), stomach (12.3%; 70/568), duodenum (3.5%; 20/566) and terminal ileum (6.2%; 35/563). Terminal ileum disease, so called "backwash ileitis" was only present in children with extensive colitis (E3).

5.4.5.3: p-ANCA Positivity and its Associated Significance

A third of UC children (221/631) had p-ANCA serology reported in the database. Of which 133 (60.2%) were positive. The p-ANCA positive children were significantly older at diagnosis with a median age of 12.6 years (IQR: 8.6, 14.3) compared to the p-ANCA negative group with a median age of 10.6 years (IQR: 6.9, 13.2; p 0.0034). There were significant differences in the frequency of p-ANCA positivity according to diagnostic age with 42.9% being positive when diagnosed at less than 6 years of age compared to 63.4% in older children (6-17yrs; p 0.0363), and a greater difference compared to those diagnosed at 12-17 years of age (71.6%; p 0.004). Positivity for p-ANCA was present in 30% of those with proctitis (E1), 69.2% of children with left sided colitis (E2) and 60% with extensive colitis (E3). Logistic regression modelling revealed that older age at diagnosis (p=0.001) and disease extent beyond the rectum (E2/E3; p=0.018) was associated with p-ANCA positivity. There were no significant association between p-ANCA positivity and gender, symptoms duration prior to diagnosis or first degree family history of IBD.

5.4.6: Inflammatory Bowel Disease Unclassified (IBDU)

There were 223 children diagnosed with IBDU. Children with IBDU were diagnosed at a younger age compared to CD (10.7yrs vs 12.2yrs; p<0.0001; table 5.4.2). The disease phenotype of these children is presented in table 5.4.7. Majority of the children presented with extensive colitis (E3) with a frequency of 77.1% compared to 17.4% with left sided colitis (E2) and 5.5% with proctitis (E1). A third of the children had involvement of their stomach and one fifth had terminal ileum disease. Over half of the children tested were p-ANCA positive.

Table 5.4.7: Phenotypic characteristics of children diagnosed with IBDU.

	IBDU
Nos of children	223
Extent of colonic disease	
Proctitis (E1)	12 (5.5%)
Left sided colitis (E2)	38 (17.4%)
Extensive colitis (E3)	168 (77.1%)
Other anatomical sites of disease:	
Orofacial	0
Oesophagus	18 (8.9%)
Stomach	74 (36.6%)
Duodenum	30 (15.1%)
Jejunum	2 (1.2%)
Ileum	8 (4.8%)
Terminal ileum	45 (22.7%)
Perianal disease	9 (4.2%)
Granuloma at any site	10 (7.5%)
1st degree family history of IBD	22 (10.7%)
EIMs	60 (27.5%)
ASCA IgA positivity (nos tested=19)	2 (10.5%)
ASCA IgG positivity (nos tested=19)	4 (21.1%)
p-ANCA positivity (nos tested=49)	27 (55.1%)

5.4.7: Positive First Degree Family History of IBD

There were 9.6% of children (189/1975) at diagnosis who had a first degree relative with IBD. The frequencies among the disease subtypes were 10% for CD, 8.2% for UC and 10.7% for IBDU. There were no significant differences in diagnostic age, disease distribution and behaviour between children with a positive first degree family history compared to the rest of the cohort.

5.4.8: Laboratory Parameters

The laboratory parameters at diagnosis are presented in table 5.4.8. There were statistically significant differences in laboratory results between the disease subtypes but these differences were not thought to be clinically relevant.

Table 5.4.8: Laboratory parameters at diagnosis (median; IQR).

	CD	UC	IBDU
Hb (g/L)	113[b] (10.2, 12.5)	117[c] (9.9, 12.9)	12.1[b,c] (10.5, 13.2)
PCV (L/L)	35 (32, 38)	36 (30, 39)	36 (32, 39)
Platelets (10^9/L)	458[a,b] (361, 580)	403[a,c] (325, 509)	368[b,c] (295, 449)
WCC (10^9/L)	9.2[b] (7.4, 11.9)	9.6[c] (7.6, 12.1)	8.4[b,c] (6.6, 10.5)
ESR (mm/hr)	32[a,b] (16, 51)	20[a,c] (10, 40)	15[b,c] (7, 35)
CRP (mg/L)	19[a,b] (5, 51)	5[a,c] (3, 16)	5[b,c] (1, 7)
Albumin (g/L)	35[a,b] (30, 39)	38[a,c] (34, 42)	40[b,c] (36, 43)
ALT (U/L)	16[a,b] (10, 24)	19[a] (12, 30)	20[b] (14, 27)
GGT (U/L)	15 (10, 21)	14 (10, 25)	14 (11, 22)

[a]CD vs UC $p<0.05$; [b]CD vs IBDU $p<0.05$; [c]UC vs IBDU $p<0.05$.
g/L: gram/litre; mg/L: milligram/litre; L/L: litre/litre; mm/hr: mm per hour; U/L: Units/litre.

5.4.9: Discussion

5.4.9.1: Predominance of Crohn's Disease

CD was the predominant disease subtype in Australian children with a frequency of 59.4% (table 5.4.1). This was similar to New Zealand where there was also a predominance of CD (34/52; 66%).[50] Beyond Australasia, CD was diagnosed more often than UC or IBDU in children, with the exception of Finland,[31, 32] Italy,[34] and Poland.[10]

CD remained the predominant disease subtype between 1996 and 2009 in Australia. Earlier paediatric studies from other countries have demonstrated that UC was the more likely diagnosis but now the incidence of CD has risen dramatically whilst UC has remained stable or fallen. This was demonstrated in Scotland,[58] Sweden,[14, 22] and Italy.[34] This change in incidence was not shown in this study because data collection began in 1996, and thus had the study extended earlier then a similar trend may have been present.

5.4.9.2: Age-related Changes in Disease Subtype

Within this Australian paediatric cohort, there was an equal proportion of CD and UC in those aged less than six years, with a dramatic increase in the frequency of CD compared to UC and

IBDU beyond this age (figure 5.4.1 and 5.4.2). This trend has been demonstrated in other studies, with a greater rise in CD over UC from 6-8 years of age.[25, 67, 68, 70, 71]

Misclassification of IBD into UC over CD in the younger age group could be possible due to the high frequency of isolated colonic disease seen in children aged less than eight years.[67, 68, 130] Similarly this current study demonstrated that children with CD, aged less than six years had a significantly greater frequency of isolated colonic disease (L2; 50%) compared to the 6-17 years cohort (31.4%; p=0.0004). Thus, younger children with isolated colitis were more likely to be classified as UC or IBDU, despite the potential for their disease to evolve into small bowel CD with increasing age.[68, 69, 72, 75, 130] Therefore, physicians managing such young patients need to have a low threshold for disease re-evaluation.

5.4.9.3: Gender related Differences in Disease Subtype

Interrogation of the Australian IBD data using APAIBD has demonstrated a male predominance in children diagnosed with CD that was significantly greater than the background age matched paediatric Australian population.[451] The male to female ratio of 1.4:1 in children diagnosed with CD in this study was within the published range from other studies of 1.2-1.8.[6, 9, 22, 25, 37, 39, 70, 75, 76]

This male predominance of childhood onset CD was greater in children diagnosed at less than six years of age (68.9%) compared to the older children (57.9%; p=0.037). This age related gender difference has not been demonstrated in other paediatric studies.[70, 71] The study by Gupta et al[71] demonstrated that 63.3% of their children with CD aged 0-5 years were male compared to 56.6% in those age 6-17 years (p=0.24). Furthermore, there does appear to be a reversal in gender predominance with more females being diagnosed with CD from late adolescence onwards.[6, 19, 20, 75-77] Vernier-Massouille et al[76] from Northern France demonstrated a change in male predominance from 1.41:1 in children with CD diagnosed prior to 15 years of age to 0.94:1 in those diagnosed between 15-17 years of age (p=0.04). In contrast, male predominance persisted at all ages in Australian children with CD.

There was a male predominance in both UC (1.12:1) and IBDU (1.21:1), but this was not significantly different to the gender distribution of the background Australian age matched paediatric population.[451]

5.4.9.4: Crohn's Disease

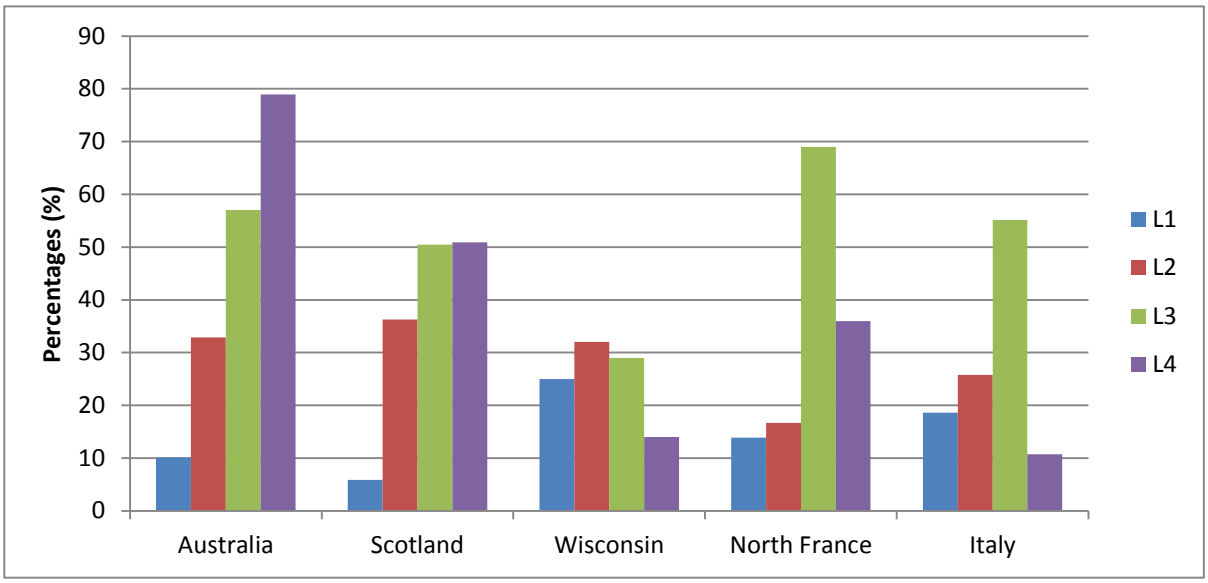
5.4.9.4.1: Anatomical Distribution of Crohn's Disease

It was interesting to note that a large proportion of Australian children presented with disease proximal to the terminal ileum (L4; 78.9%), which was greater than that reported in other large series (figure 5.4.5).[25, 34, 75, 76] A similar study with a high frequency of upper gastrointestinal disease was that from Scotland where half of their children had disease involvement proximal to the terminal ileum.[75] One possible reason for this may be the fact that all upper gastrointestinal lesions were included, such as erythema, loss of vascular pattern, cobble-stoning, ulceration and histological inflammation. Within the database, no details on the type or severity of the lesions were recorded, unlike that of the colon and terminal ileum.

Upper gastrointestinal disease (L4) was associated with terminal ileum and/or colonic disease in 778 (95.3%) children, which left 38 (4.7%) presenting with isolated upper gastrointestinal disease (L4). This was slightly higher than the 2.2% demonstrated in Scottish children by Van Limbergen et al.[75] This finding reinforces the importance of undertaking an upper gastrointestinal endoscopy and small bowel imaging, such as ultrasound, barium study and magnetic resonance enterography, in order to obtain a complete picture of disease distribution.

Over half of the Australian children with CD presented with ileocolonic disease (L3), similar to cohorts from Scotland,[75] Italy,[34] United States[124] and Northern France[76] (figure 5.4.5). There was a significant association between upper gastrointestinal (L4) and ileocolonic (L3) disease with 503 out of the 996 children (50.5%; $p<0.0001$). This was greater than the 27% reported from the Scottish cohort.[75]

Figure 5.4.5: Disease distribution according to the Montreal classification among various paediatric cohorts.[25, 34, 75, 76]



5.4.9.4.2: Influence of Age on Disease Distribution

Half of the younger children, aged less than six years at diagnosis, presented with isolated colonic disease (L2) (figure 5.4.3). With increasing age at diagnosis, there was a significant decrease in the frequency of isolated colonic disease (L2) and an increase in terminal ileal involvement, contributing towards increased frequency of both isolated terminal ileal (L1) and ileocolonic (L3) disease. This was in keeping with previous studies demonstrating this change in distribution with increasing age.[67, 68, 75, 130]

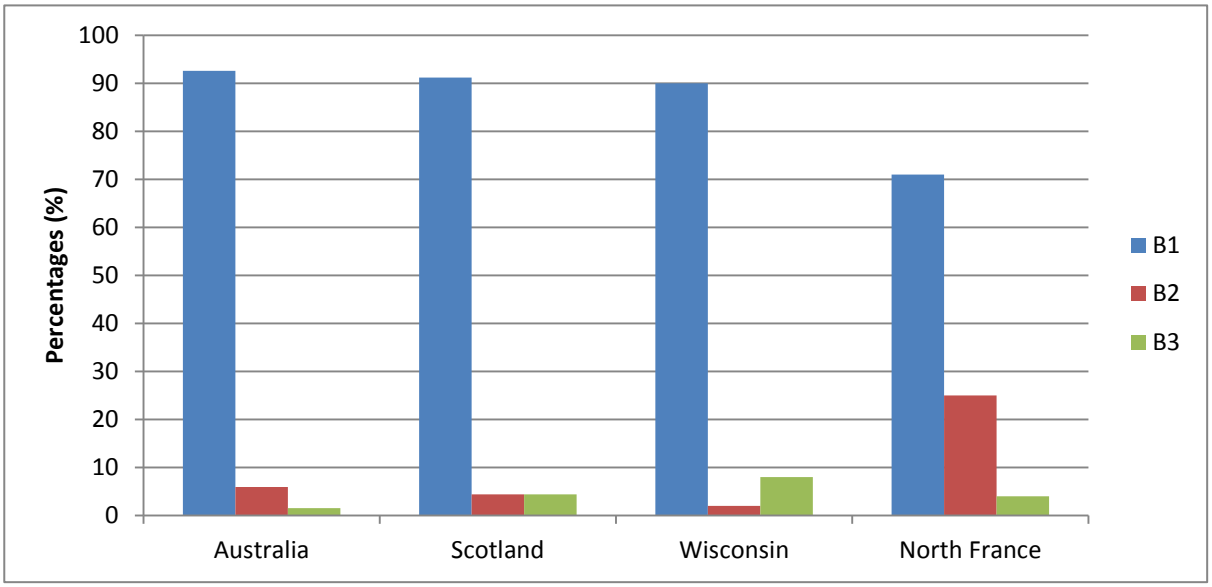
With increasing age up to mid-adulthood, the disease may extend to involve the small intestine. Thereafter, there is less upper gastrointestinal disease (L4), less panenteric disease involvement (L3+L4) and greater frequency of isolated colonic (L2) or isolated ileal disease (L1).[75, 118, 119, 131-133] The Scottish study by Van Limbergen et al[75] demonstrated that children had a significantly greater panenteric (L3+L4), ileocolonic (L3) and upper gastrointestinal (L4) involvement and significantly less isolated ileal (L1) disease compared to adults. The study by Polito et al[119] demonstrated that patients diagnosed with CD at less than 20 years of age have significantly greater frequency of small bowel and oesophageal/gastric/duodenal disease and significantly less colonic disease compared to those diagnosed at 40 years of age or older.

5.4.9.4.3: Behaviour of Crohn's Disease at Diagnosis

This current study demonstrated that the majority of Australian children presented with inflammatory behaviour (B1; 92.6%), similar to other published paediatric cohorts (figure 5.4.6).[25, 75, 76] It was interesting to note that 25% of children from Northern France presented with stricturing intestinal behaviour (B2) which was greater than the 5.9% demonstrated in this current study and higher than 2-4.4% in other studies.[25, 75, 76]

The association of inflammatory (B1) and stricturing (B2) behaviour with isolated colonic (L2) and terminal ileum disease (L1 and L3) respectively was reproduced in this study, confirming similar associations found by other studies.[119, 165] This relationship remained significant on logistic regression even when other independent factors were analysed such as age at diagnosis, other specific anatomical sites of disease and serology. This association may highlight differences in the nature of inflammation among the various anatomical sites.

Figure 5.4.6: Comparison of disease behaviour at diagnosis between APAIBD and other paediatric cohorts.[25, 75, 76]



5.4.9.4.4: Importance of Granulomata in Crohn's Disease

The frequency of granulomata detected was low (19.1%) compared to the range reported in other paediatric studies of 19.7 to 67.2%.[11, 13, 71, 124, 232, 255, 256, 259-262] The differences in reported frequencies among various studies may be related to the histopathologist's definition of a Crohn's granuloma, their skill in detecting such lesions, the number of biopsies at various sites and the number of histological sections of each biopsy.[232, 254, 255] Unless this is standardised then comparison among various studies may be limited.

The higher rates of granulomata in orofacial biopsies (48.3%) and perianal disease have been reported in other studies.[157, 159, 161-163, 232, 263, 264] What was unique in this study was the significantly increased frequency of granulomata in boys compared to girls (22.8% vs 13.8%). This increased frequency in boys was independent of other positive associations, such as orofacial and perianal disease, gastrointestinal tract involvement and disease behaviour on logistic regression analysis. In addition, the association between the presence of granulomata with inflammatory behaviour (B1) and less stricturing disease (B2) in this Australian cohort was interesting and worthy of further research.

5.4.9.4.5: Importance of ASCA Serology in Crohn's Disease

The proportion of children with CD who had ASCA testing was quite low at 12.9%, given that this test was recently introduced in 2005 and increasingly ordered. Just under half of Australian children with CD who were tested were positive for ASCA IgA (47.8%) and IgG (49.7%). This was within the lower reported range of 40 to 86% in other studies.[227, 229-238]

ASCA positivity was associated with terminal ileal disease, upper gastrointestinal disease (proximal ileum) and a slightly but significantly older age at diagnosis. The older age at diagnosis was confounded by disease distribution, since on logistic regression modelling, significance of the age was lost when analysed with disease distribution (table 5.4.5). The significant association between disease of the ileum and ASCA positivity has been demonstrated in several studies.[229, 239-246] Unlike the study by Russell et al,[237] ASCA positivity was associated with low albumin on direct analysis but not on multivariate logistic regression. In addition, there was no association with orofacial lesions in this analysis, contrasting to the study by Russell et al[237] where ASCA positivity was associated with oral lesions (table 5.4.5). Within this Australian cohort, there was no association between ASCA positivity and complicated disease behaviour unlike that reported in the literature.[229, 239-245, 247-249] This may be due to the small sample size of children tested and the database recorded information at diagnosis, without any longitudinal data on subsequent complicating behaviour.

5.4.9.4.6: Significance of p-ANCA Positivity in Crohn's disease

One fifth of the tested CD cohort was positive for p-ANCA which was within the range of 5 to 32% reported in the literature.[227, 229-231, 234, 236, 238, 246, 247] This study reinforced the

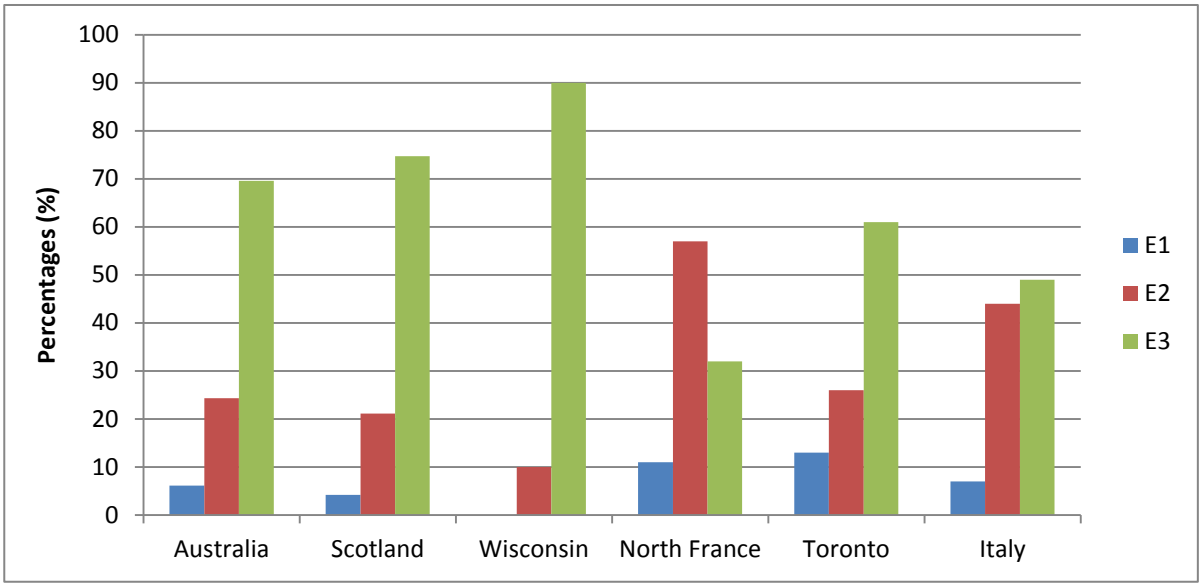
uniqueness of p-ANCA positive CD children presenting with isolated colonic disease.[229, 234, 246, 247, 250] What was new in this study was that p-ANCA positivity was associated with a lower frequency of perianal disease. Finally, the association of p-ANCA positivity with an increased first degree family history of IBD was interesting.

5.4.9.5: Ulcerative colitis

5.4.9.5.1: Colonic Extent of Disease in Australian Children

The majority of children presented with extensive disease (E3) with a frequency of 70% and only 6% presented with proctitis (E1), similar to other paediatric cohorts (figure 5.4.7). Higher rates of extensive colitis were reported from Wisconsin[25] and Scotland[75] with reported frequencies of 90% and 75% respectively.

Figure 5.4.7: Comparison of colonic disease extent in APAIBD children with other paediatric cohorts.[6, 13, 25, 34, 75]



5.4.9.5.2: Age-related Differences in Disease Extent

Within this Australian paediatric cohort there was a significantly increasing frequency of proctitis with older age at diagnosis, which has not been reported previously within a paediatric population (figure 5.4.6).[34, 67, 120] It would appear that this trend may continue into adulthood, since adults are more likely to present with proctitis (E1; 44-49%) and less extensive colitis (E3; 14-37%) compared to children.[8, 75, 122, 135, 136]

5.4.9.5.3: Importance of p-ANCA Positivity in Ulcerative Colitis

Sixty percent of the tested children with UC were p-ANCA positive which was in keeping with the reported rates of 57-82%.[120, 226, 227, 234, 236, 238] This study demonstrated that there was a significant association between positivity for p-ANCA and increasing diagnostic age and disease extending beyond the rectum (E2/E3).[238]

5.4.9.6: Inflammatory Bowel Disease Unclassified

Overall, 10% of the Australian children with IBD were labelled as IBDU. In the young children aged less than six years at diagnosis, the proportion was greater at 17.2% (figure 5.4.2). This was lower than other studies where the proportion of children diagnosed as IBDU may be as high as 30% in those aged less than five years, decreasing to around 10% in adolescence and adulthood.[68, 72] This cohort of children is interesting since they represent undifferentiated disease, which over the next two years may evolve into CD or UC.[68, 72]

5.4.10: Conclusion

The phenotype of Australian children diagnosed with IBD is similar to other reported international cohorts. There is a clear change in phenotype with increasing age in both CD and UC, continuing into adulthood. These differences may reflect changes in the immunological response to environmental factors, the mucosal integrity and the impact of the microbiome population.

5.5: Orofacial Crohn's Disease

5.5.1: Analysis of Orofacial Crohn's Disease

Within the CD cohort, details on the presence or absence of orofacial disease (OFD) were recorded in 1207 children (97%). There were 107 children who presented with orofacial disease (8.9%). Details on the phenotypic features at diagnosis are presented in table 5.5.1.

Table 5.5.1: Phenotypic features at diagnosis of children with orofacial CD (OFD) compared to the rest of the cohort.

	OFD	**Non-OFD**	**p-value**
Number of Children	107	1100	
Age at diagnosis (IQR)	10.4yrs (8.1, 13.5)	12.2yrs (9.8, 14.3)	**0.0001**
Gender (male proportion)	66 (n=107; 61.7%)	643 (n=1100; 58.5%)	0.59
Duration of symptoms prior to diagnosis (IQR)	26wks (12, 52)	22wks (9, 52)	0.0056
First degree family history of IBD	7 (n=103; 6.8%)	106 (n= 1048; 10.1%)	0.36
Pre- or early puberty (Tanner stage 1-2)	64 (n=81; 79%)	525 (n=737; 71.2%)	0.18
EIMs	86 (n=107; 80.4%)	409 (n=1093; 37.4%)	**<0.0001**
Disease Distribution	N=93	N=1061	
Isolated terminal ileum (L1)	10 (10.8%)	104 (9.8%)	0.910
Isolated colonic (L2)	34 (36.6%)	345 (32.5%)	0.496
Ileocolonic (L3)	49 (52.7%)	612 (57.7%)	0.409
Upper gastrointestinal tract (L4)	61 (n=91; 67%)	752 (n=937; 80.3%)	**0.0047**
Perianal disease	79 (n=105; 75.2%)	463 (n=1072; 43.2%)	**<0.0001**
Disease behaviour	N=107	N=1097	
Inflammatory (B1)	100 (93.5%)	1015 (92.5%)	0.874
Stricturing (B2)	7 (6.5%)	64 (5.8%)	0.935
Penetrating (B3)	0%	18 (1.6%)	0.359

5.5.1.1: Age related Differences

Children with orofacial lesions presented approximately 2 years younger than the rest of the cohort (table 5.5.1). There were gender differences in age at diagnosis. Males with orofacial lesions presented 3 years younger (median age of 9.3 years; IQR: 7, 13) than the other males (median age: 12.4 years; IQR: 9.7, 14.5; p=0.0001). On the other hand, there were no differences in the age at diagnosis in females with and without OFD (11.4 years with OFD vs 12.1 years without OFD; p=0.27). When analysed according to the 6 year division, there was a significant decrease in frequency of orofacial disease in males aged 12 years or older (table 5.5.2).

Table 5.5.2: Frequency of OFD according to the 6 years age group.

Age group	**Females (n=41)**	**Males (n=66)**	**Total (n=107)**
<6yrs	1 (2.4%)	11 (16.7%)[a]	12 (11.2%)
6-11yrs	22 (53.7%)	34 (51.5%)[c]	56 (52.3%)[b]
12-17yrs	18 (43.9%)	21 (31.8%)[a,c]	39 (36.4%)[b]

[a]p=0.0046; [b]p=0.0022; [c]p=0.003

5.5.1.2: Anatomical Extent of Disease

There were no significant association between the presence of orofacial lesions and disease involvement of the terminal ileum and colon. However, children with orofacial lesions had a significantly lower frequency of upper gastrointestinal CD (67% vs 80%; table 5.5.1). Within the upper gastrointestinal disease, there was a significant positive association between orofacial and oesophageal involvement and a negative relationship with gastric and duodenal involvement (table 5.5.3). On multivariate logistic regression modelling, the presence of oesophageal disease was associated with increased risk of orofacial CD whilst gastric disease was associated with a reduced risk of orofacial disease (table 5.5.3).

Table 5.5.3: Frequency of disease within the upper gastrointestinal tract in children with orofacial CD (OFD).

				Multivariate logistic regression	
Disease involvement	**OFD**	**Non-OFD**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Oesophagus	32 (n=101; 31.7%)	204 (n=1051;19.4%)	**0.0053**	3.3 (1.8, 6)	**0.0001**
Stomach	43 (n=103; 41.7%)	602 (n=1057; 57%)	**0.004**	0.36 (0.2, 0.65)	**0.0007**
Duodenum	16 (n=100; 16%)	274 (n=1037; 26.4%)	**0.031**	0.76 (0.36, 1.6)	0.48
Jejunum	6 (n=75; 8%)	59 (n=802; 7.4%)	0.98	1.18 (0.41, 3.38)	0.76
Proximal ileum	18 (n=76; 23.7%)	201 (n=806; 24.9%)	0.92	0.85 (0.44, 1.64)	0.62

5.5.1.3: Association with Disease Behaviour

There were no significant association between orofacial lesions and intestinal disease behaviour (table 5.5.1).

5.5.1.4: Association with Perianal Disease

Orofacial disease at diagnosis was associated with perianal disease, especially anal tags and fissures (table 5.5.4). This association was present in both genders but the frequency was greater in males compared to females (table 5.5.5). On multi-logistic regression modelling for the presence of orofacial disease (OFD) with diagnostic age, gender, specific perianal lesions, Montreal distribution of disease and behaviour as independent factors, the significant association with anal tags (p=0.0007) and anal fissures (p=0.05) was maintained.

Table 5.5.4: Frequency of perianal disease in children with OFD.

	OFD (n=105)	**Non-OFD (n=1072)**	**p-value**	**CD cohort (n=1177)**
Perianal disease	79 (75.2%)	463 (43.2%)	< **0.0001**	542 (46%)
Anal tags	56 (53.3%)	281 (26.2%)	< **0.0001**	337 (28.6%)
Anal fissures	56 (53.3%)	308 (28.8%)	< **0.0001**	364 (31%)
Perianal ulcer	5 (4.8%)	20 (1.9%)	0.06	25 (2.1%)
Perianal fistula	9 (8.6%)	70 (6.5%)	0.55	79 (6.7%)
Perianal abscess	10 (9.5%)	76 (7.1%)	0.47	86 (7.3%)

Table 5.5.5: Frequency of perianal disease with OFD among male and female children.

	OFD	Non-OFD	p-value	CD cohort
Female children	41	444		485
Perianal disease	27 (65.9%)	184 (41.4%)	**0.004**	211 (43.5%)
Anal tags	20 (48.8%)	141 (31.8%)	**0.041**	161 (33.2%)
Anal fissure	18 (43.9%)	113 (25.5%)	**0.018**	131 (27%)
Perianal ulcer	0	11 (2.5%)	0.64	11 (2.3%)
Perianal fistula	0	15 (3.4%)	0.26	15 (3.1%)
Perianal abscess	2 (4.9%)	12 (2.7%)	0.33	14 (2.9%)
Male children	64	628		692
Perianal disease	52 (81.3%)	279 (44.4%)	**<0.0001**	331 (47.8%)
Anal tags	36 (56.3%)	140 (22.3%)	**<0.0001**	176 (25.4%)
Anal fissure	38 (59.4%)	195 (31.1%)	**<0.0001**	233 (33.7%)
Perianal ulcer	5 (7.8%)	9 (1.4%)	**0.006**	14 (2%)
Perianal fistula	9 (14.1%)	55 (8.8%)	0.24	64 (9.2%)
Perianal abscess	8 (12.5%)	64 (10.2%)	0.72	72 (10.4%)

5.5.1.5: Association between Orofacial CD and Extra-intestinal manifestations

The presence of orofacial CD was associated with both ocular and dermatological EIMs, which were independent of each other on logistic regression modelling (table 5.5.6). This association with ocular EIMs was maintained in both males and females but the significant dermatological association was found only in males. Further analysis of specific ocular and dermatological lesions was limited by the small number of children.

Table 5.5.6: Frequency of extra-intestinal manifestations in children with orofacial disease.

	OFD (n=107)	**Non-OFD (n=1093)**	**p-value**	**CD cohort (n=1200)**
EIMs	86 (80.4%)	409 (37.4%)	**<0.0001**	495 (41.3%)
Hepatobiliary	2 (1.9%)	55 (5%)	0.22	57 (4.8%)
Musculoskeletal	14 (13.1%)	146 (13.4%)	0.94	160 (13.3%)
Ocular	8 (7.5%)	19 (1.7%)	**0.0016**	27 (2.3%)
Dermatological	16 (15%)	66 (6%)	**0.001**	82 (6.8%)

5.5.1.6: Presence of Granulomata in Orofacial CD

Within the cohort of orofacial CD, 39 (36%) had undergone orofacial biopsies, of which 33 (84.6%) had granulomata on histology. It was interesting that 19 children with orofacial granulomata had no other gastrointestinal granulomata detected on endoscopic evaluation.

5.5.1.7: Laboratory Abnormalities in Children with Orofacial CD

There were statistically significant differences in laboratory parameters in children with orofacial CD but these were not clinical relevant (table 5.5.7).

Table 5.5.7: Comparison of laboratory parameters in OFD compared to non-OFD (median, IQR; number of children).

	OFD	Non-OFD	p-value
Hb (g/L)	118 (105, 125) (n=92)	113 (102, 125) (n=1013)	0.0353
PCV (L/L)	35 (32, 38) (n=92)	35 (32, 38) (n=1013)	0.5911
Plts (10^9/L)	462 (365, 593) (n=92)	432 (341, 499) (n=1013)	0.0523
WCC (10^9/L)	9.27 (7.35, 11.25) (n=92)	9.3 (7.45, 12) (n=1013)	0.2822
ESR (mm/hr)	25 (11, 42) (n=87)	33 (17, 52) (n=950)	0.0111
CRP (mg/L)	21 (5, 53.5) (n=82)	12 (5, 26) (n=912)	0.0077
Albumin (g/L)	34 (29, 39) (n=92)	35 (30, 39) (n=983)	0.7224
ASCA IgA positivity	8 (n=24; 33.3%)	68 (n=136; 50%)	0.1267
ASCA IgG positivity	10 (n=24; 41.7%)	69 (n=136; 50.7%)	0.1961
p-ANCA positivity	7 (n=39; 17.9%)	59 (n=301; 19.6%)	0.5017

5.5.1.8: Anthropometric Data in Children with Orofacial Crohn's Disease

Children with orofacial lesions at diagnosis of CD presented with a better weight and BMI z-score than those without such lesions (table 5.8.1).

5.5.2: Discussion of Orofacial Crohn's Disease

5.5.2.1: Frequency of Orofacial Lesions

The overall frequency of orofacial lesions within the cohort of children diagnosed with CD was 8.9%, which was within the reported range of 0.5-9%.[21, 70, 75, 156, 158] This frequency may been higher if dentists or oral surgeons reviewed these children, as they were more likely to identify orofacial abnormalities than gastroenterologists.[157, 161] The frequency of orofacial lesions increased to 41-48% of Irish children with CD, when examined by a dentist with nearly half of the children missed by a gastroenterologist.[157, 161]

Unfortunately, the database does not record data on the type of orofacial lesion. This was important as there may have been variable lesions found which may have differing relationship with disease extent, behaviour, extra-intestinal manifestations and laboratory parameters. Orofacial involvement in CD can be diverse and include gingivitis, mucosal tags, ulceration, lip swelling and cobble-stoning.

5.5.2.2: Age and Gender related Differences

Children with orofacial disease were diagnosed at a younger age compared to those without orofacial involvement, and the difference was due to the males and not females. It appeared that this age related difference was only present in males as the frequency significantly decreased with increasing diagnostic age (table 5.5.2). The duration of symptoms prior to diagnosis was significantly longer in the orofacial group but the difference was not thought to be clinically relevant (table 5.5.1). Similarly, younger age at diagnosis and increased duration of disease prior to diagnosis was reported in a paediatric study from the United Kingdom and Ireland.[70]

Other studies have shown that orofacial Crohn's predominated in male children which was not reproduced in this Australian cohort.[156, 157, 159, 161] What was interesting was that boys with orofacial Crohn's demonstrated a stronger association with other phenotypic features compared to the girls.

5.5.2.3: Association with Disease Distribution

There was a significant association between the presence of orofacial lesions and oesophageal disease, which was independent of other possible associations (table 5.5.3). No other studies have shown this association to be significant. The study by Pittock et al,[161] revealed that 5 of their 12 children with oral CD had oesophageal and/or gastric inflammation, while Dupuy et al[156] found 3 of the 9 reported with orofacial CD had inflammation of the oesophagus.

There was a significant association between orofacial and perianal disease. Three quarters of the children with orofacial CD had perianal disease at diagnosis compared to just under half of those without orofacial lesions (table 5.5.1). Other studies have shown a higher frequency of perianal disease, but only the study by Harty et al[157] demonstrated a significant relationship.[156-159] Further analysis of perianal disease demonstrated that orofacial disease was associated with anal tags and fissures, and not fistula, abscess or ulcers (table 5.5.4). The

exact type of orofacial lesions were not recorded as it would have been interesting to explore this relationship further. This association was stronger for males compared to females, which has not been demonstrated in other studies (table 5.5.5).

5.5.2.4: Association with Ocular and Dermatological Extra-Intestinal Manifestations

The significant association between orofacial lesions and ocular and dermatological manifestations has not been described previously and needs further research. Questions should include the genetics, nature of the inflammatory response, and details about the type of orofacial involvement. Such children with orofacial lesions may need early ophthalmology and dermatology review. Further analysis of the relationship with specific ocular and dermatological lesions was limited by the small number of children.

5.5.2.5: Importance of Orofacial Biopsies and Relevance of Granulomata

This study stressed the importance of undertaking orofacial biopsies in establishing a diagnosis and sub-classifying as CD, since 33 of the 39 children (85%) had granulomata on histology. This high rate of granulomata was in keeping with previous studies reporting rates of 66 to 100%.[157, 159, 161-163] In 19 of the 33 children with granulomatous orofacial disease, there were no gastrointestinal granulomata detected elsewhere, raising the concern that had these orofacial biopsies not been taken, then their disease may have been misclassified. Previous studies have shown that non-caseating granulomata were found in biopsies from areas of gingivitis, tags, ulcers and cobble-stoning, however this data was not recorded in the current study cohort.[157, 161]

5.5.3: Conclusion

This analysis of the Australian paediatric and adolescent IBD database (APAIBD) has highlighted the uniqueness of children with orofacial CD. Such children represent a distinct phenotype with inflammation of the squamous epithelium. The association with perianal disease, oesophageal inflammation, ocular and dermatological extra-intestinal lesions has been established in this large Australian wide cohort. Identification of orofacial lesions in children with IBD will help in exploring the possibility of CD and targeting therapy accordingly.

5.6: Perianal Crohn's Disease

5.6.1: Analysis of Perianal Crohn's Disease

Of the children diagnosed with CD, 1184 (95%) had details on the presence or absence of perianal disease recorded. Perianal disease was present in 545 children (46%) at diagnosis and specific lesions are presented in table 5.6.1. The most common lesions were anal fissures (30.9%) and tags (28.5%), followed by perianal fistula (6.8%) and abscess (7.4%). The phenotypic features at diagnosis are presented in table 5.6.2.

Table 5.6.1: Frequency of perianal disease in CD.

	Number of children
Total CD cohort	1184
Any perianal disease	545 (46%)
Anal fissure	366 (30.9%)
Anal tags	338 (28.5%)
Perianal ulcer	25 (2.1%)
Perianal fistula	81 (6.8%)
Perianal abscess	87 (7.3%)

Table 5.6.2: Phenotypic details of children presenting with perianal disease compared to the rest of the cohort.

	Perianal disease (n=545)	**No Perianal disease (n=639)**	**p-value**
Age at diagnosis (IQR)	12.3yrs (10, 13.9)	12yrs (9.5, 14.3)	0.25
Males	333 (61.1%)	365 (57.1%)	0.18
Duration of symptoms prior to diagnosis (IQR)	26wks (12, 52)	22wks (9, 52)	**0.01**
First degree family history of IBD	54 (10.4%)	58 (9.5%)	0.67
Pre- or early puberty (Tanner stage 1-2)	278 (72.6%)	301 (71%)	0.67
EIMs	251 (46.1%)	231 (36.2%)	**0.0007**
Disease Distribution			
Orofacial disease (OFD)	79 (14.6%)	26 (4.1%)	**<0.0001**
Upper gastrointestinal (L4)	381 (80.9%)	418 (77.1%)	0.16
Isolated terminal ileum (L1)	41 (8.1%)	72 (11.6%)	0.065
Isolated colonic (L2)	138 (27.2%)	240 (38.5%)	**<0.0001**
Ileocolonic (L3)	329 (64.8%)	311 (49.9%)	**<0.0001**
Disease behaviour			
Inflammatory (B1)	494 (90.6%)	604 (94.7%)	0.0104
Stricturing (B2)	41 (7.5%)	29 (4.5%)	**0.0414**
Penetrating (B3)	10 (1.8%)	5 (0.8%)	0.177

5.6.1.1: Strong Relationship between Perianal Lesions

Various perianal lesions were associated with each other (table 5.6.3). The strongest association was between anal tags and fissures (chi-square: 221, $p<0.0001$), and between perianal fistula and abscess (chi-square: 137, $p<0.0001$).

Table 5.6.3: Association between various perianal lesions in a multi-logistic regression analysis (odds ratio with 95% confidence interval).

Perianal lesion	**Anal tag**	**Anal fissure**	**Perianal ulcer**	**Perianal fistula**	**Perianal abscess**
Independent variables					
Anal tag		**OR: 7.5 (5.6, 10) p<0.0001**	**OR: 3.9 (1.5, 9.7) p=0.004**	OR: 1 (0.6, 1.8) p=0.99	OR: 0.9 (0.5, 1.5) p=0.69
Anal fissure	**OR: 7.5 (5.6, 10.1) p<0.0001**		OR: 1.2 (0.5, 2.9) p=0.74	**OR: 2.4 (1.4, 4.1) p=0.002**	**OR: 2.7 (1.6, 4.5) p=0.002**
Perianal ulcer	**OR: 3.9 (1.5, 9.7) p=0.004**	OR: 1.2 (0.4, 3.2) p=0.78		OR: 2.4 (0.8, 7.5) p=0.12	**OR: 3.6 (1.3, 10.2) p=0.014**
Perianal fistula	OR: 1 (0.6, 1.8) p=0.96	**OR: 2.3 (1.4, 4) p=0.0023**	OR: 2.7 (1, 7.8) p=0.06		**OR: 10.1 (5.9, 17.4) p<0.0001**
Perianal abscess	OR: 0.8 (0.5, 1.5) p=0.54	**OR: 2.7 (1.6, 4.6) p=0.0002**	**OR: 3.6 (1.3, 10.1) p=0.01**	**OR: 10.2 (5.9, 17.5) p<0.0001**	

5.6.1.2: Age related Differences in Frequency

There were no differences in the median age at diagnosis in those with perianal lesions (table 5.6.2), but there was a significantly lower frequency of anal tags in both boys and girls aged less than 6 years (table 5.6.4).

Table 5.6.4: Age related frequency of perianal lesions.

Age at diagnosis	**Less than 6 years (n=98)**	**6-17 years (n=1086)**	**Total (n=1184)**
Any perianal lesions	32 (32.7%)[a]	513 (47.2%)[a]	545
Anal tag	13 (13.3%)[b]	325 (29.9%)[b]	338
Anal fissure	25 (25.5%)	341 (31.4%)	366
Perianal ulcer	1 (1%)	24 (2.2%)	25
Perianal fistula	5 (5.1%)	76 (7%)	81
Perianal abscess	5 (5.1%)	82 (7.6%)	87

[a]p=0.0076; [b]p=0.0007

5.6.1.3: Gender related Differences in Perianal Lesions

Despite there being no gender related differences in the overall frequency of perianal lesions, the frequency of anal tags was significantly higher in females, while males had a significantly higher frequency of anal fissures, perianal fistulae and abscess formation at diagnosis (table 5.6.5).

Table 5.6.5: Gender related differences in the frequency of perianal lesions.

	Females	**Males**	**Number of children with CD**
Overall CD cohort	486	698	1184
Any perianal lesion	212 (43.6%)	333 (47.7%)	545
Anal tag	162 (33.3%)[a]	176 (25.2%)[a]	338
Anal fissure	132 (27.2%)[b]	234 (33.6%)[b]	366
Perianal ulcer	11 (2.3%)	14 (2%)	25
Perianal fistula	15 (3.1%)[c]	66 (9.5%)[c]	81
Perianal abscess	14 (2.9%)[d]	73 (10.5%)[d]	87

[a]p=0.003; [b]p=0.02; [c]p=0.0003; [d]p<0.0001

5.6.1.4: Association between Perianal Disease and Anatomical Involvement of Crohn's Disease at Diagnosis

There was a significantly greater frequency of perianal lesions in children with ileocolonic disease (L3; 51.4%) compared to those with isolated terminal ileal (L1; 36.3%; p=0.004) and isolated colonic disease (L2; 36.5%; p<0.0001). The significant association with ileocolonic disease (L3) was present for anal tags, fissures, fistula and abscess, but not with perianal ulcers. On logistic regression analysis, rectal disease was independently associated with the presence of perianal fistula (OR: 2.2; 95% CI: 1.1, 4.3; p=0.025) when compared with other segments of colonic involvement.

Increasingly, there were significant associations between upper gastrointestinal tract disease and perianal lesions at diagnosis. Analysis according to different segments of the upper gastrointestinal tract revealed a significant association between inflammation of the oesophagus with anal tags and/or fissures, which was independent of disease elsewhere.

5.6.1.5: Relationship between Orofacial Crohn's Disease and Perianal Lesions

Presence of orofacial CD was associated with perianal disease (table 5.6.2). Detailed relationship between orofacial and specific perianal lesions was presented in section 5.5.

5.6.1.6: Impact of Intestinal Disease Behaviour on Perianal Lesions

The frequency of perianal disease was significantly greater in children with complicating intestinal behaviour (B2/B3) compared to inflammatory disease (60% vs 45%; p=0.01; table 5.6.2). On further analysis, there was a greater proportion of children with stricturing behaviour (B2) presenting with perianal disease (58.6%) compared to the inflammatory group (B1; 45%; p=0.04). In contrast, there was no difference in frequency of perianal lesions in those presenting with fistulising intestinal disease. Stricturing behaviour (B2) remained an independent predictor (OR: 1.7; 95%CI: 1, 2.9; p=0.038) for perianal disease when controlling for disease location, diagnostic age and gender on regression analysis.

Analysis of specific perianal lesions with intestinal behaviour revealed that stricturing intestinal behaviour (B2) was independently predictive of anal tags only (p=0.027), and intestinal fistulising behaviour (B3) was associated with perianal fistula (p=0.03) on logistic regression analysis with disease distribution, diagnostic age, gender and other perianal lesions as independent factors.

5.6.1.7: Association with Extra-Intestinal Manifestations (EIMs)

There was an increased frequency of extra-intestinal manifestations in those children with perianal disease (46.1% vs 36.2%; p=0.0007; table 5.6.2), which was related to mouth ulcers and skin manifestations on chi square analysis and multi-variable logistic regression (table 5.6.6). Conversely, there was a decreased likelihood of hepatobiliary disease (table 5.6.6). When analysed according to type of perianal lesion, anal fissures were associated with mouth ulcers (OR: 2.1; 95%CI: 1.6, 2.9; p<0.00001) and skin lesions (OR: 2.2; 95% CI: 1.3, 3.7; p=0.005). Anal tags were also associated with mouth ulcers (OR: 1.4; 95% CI: 1, 1.9; p=0.04).

Table 5.6.6: Frequency of specific EIMs in those children with or without perianal disease.

EIMs	Perianal disease (n=545)	No Perianal disease (n=639)	p-value
Mouth ulcers	171 (31.4%)	110 (17.2%)	**<0.0001**
Hepatobiliary	12 (2.2%)	45 (7.1%)	**0.0002**
Musculoskeletal	67 (12.3%)	87 (13.6%)	0.55
Ocular	14 (2.6%)	12 (1.9%)	0.54
Dermatological	51 (9.4%)	26 (4.1%)	**0.0004**

5.6.1.8: Laboratory Abnormalities in Children with Perianal Lesions at Diagnosis

The laboratory results among children with or without perianal disease are presented in table 5.6.7. There were statistical differences in platelet count, ESR, CRP and albumin, but the magnitude of the difference was small and probably not of clinical relevance.

With regard to serological markers, the only significant association was that children who were p-ANCA positive had a significantly lower frequency of perianal disease, independent of diagnostic age, gender, disease distribution and behaviour (table 5.6.7).

Table 5.6.7: Comparison of laboratory parameters in children with or without perianal lesions (median, IQR).

	Perianal disease (n=545)	**No Perianal disease (n=639)**	**p-value**
Hb (g/L)	113 (103, 124)	114 (102, 126)	0.32
Plts (10^9/L)	475 (384, 592)	442 (344, 575)	**0.008**
WCC (10^9/L)	9.2 (7.4, 11.7)	9.3 (7.4, 12.1)	0.46
ESR (mm/hr)	34 (20, 52)	30 (13, 50)	**0.01**
CRP (mg/L)	24 (8, 56)	16 (5, 47)	**0.003**
Albumin (g/L)	33 (29, 38)	35 (31, 41)	**<0.0001**
Number of children tested for ASCA	89	69	
ASCA IgA positivity (Nos tested=158)	44 (49.4%)	31 (44.9%)	0.68
ASCA IgG positivity	51 (57.3%)	28 (40.6%)	0.054
Number of children tested for p-ANCA	182	156	
p-ANCA positivity	21 (11.5%)	45 (28.8%)	**0.0001**

5.6.1.9: Impact of Perianal Disease upon Anthropometric Parameters

Children with perianal disease at diagnosis presented with significantly lower weight, height and BMI z-scores compared to those without any perianal lesions, perhaps underlying a more aggressive phenotype reflected in a greater impact on anthropometric parameters (table 5.8.1).

5.6.2: Discussion of Perianal Disease in Crohn's disease

5.6.2.1: High frequency of Perianal Lesions

The overall frequency of perianal lesions was 46%, which was towards the upper end of the reported range of 5 to 50%.[21, 34, 50, 59, 70, 71, 75, 89, 123, 124, 129, 144-150] The most common perianal lesions were anal fissures (31%) and anal tags (29%), followed by perianal fistula (6.8%) and abscess (7.4%), which was in keeping with other studies (table 5.6.1).[6, 25, 70, 76, 145, 146, 148] One

of the reasons for the overall higher frequency would be related to the inclusion of anal tags/fissures.

5.6.2.2: Association between Perianal Lesions

There was no surprise in the significant association between perianal fistula and abscess, given the fact that they share a similar pathophysiology with an abscess forming where the fistula tract ends within the perineum. The association between anal tags and fissures within this cohort was interesting. Anal tags and fissures may share a distinct type of inflammation.

5.6.2.3: Aged related difference in Frequency of Anal Tags

There was a significantly decreased frequency of anal tags in children aged less than six years (13.3% vs 29.9%; p=0.0007; table 5.6.4). Similarly, Gupta et al[71] reported a lower frequency of perianal disease in those aged less than six years (3.1% vs 7.6% in those aged 6-17 years), although this difference was not significant.

5.6.2.4: Gender differences in Type of Perianal Lesions

There were gender differences in the type of perianal lesions (table 5.6.4). With regard to anal tags and fissures, the magnitude of the difference was not great and not deemed clinically relevant. However, males had a three to four fold increased frequency of perianal fistula and/or abscess compared to females. This male predominance of perianal fistula has been reported previously.[124, 141, 145, 151] No confounding factors were identified to explain this male predominance.

5.6.2.5: Association with Anatomical Extent of Disease

It was interesting to note a higher frequency of perianal disease in those with ileocolonic CD, which was maintained for all types of lesions except for perianal ulcers. This has not been reported previously.

It was not surprising that rectal inflammation was associated with perianal fistula given the explanation that they usually develop from a microperforation of the nearby colon. This association has been shown by other studies, especially by Hellers et al[151] who demonstrated that the frequency of perianal fistula increased from 41% in those with colonic disease but no rectal involvement, to 91% when rectal disease was present.[148, 151, 152]

The association between anal tags and fissures with oesophageal disease, independent of orofacial CD and other anatomical involvement, has not been previously reported. The overall association between orofacial lesions, oesophageal disease and anal tags/fissures may underlie a unique form of inflammation, with predominant involvement of squamous epithelium.

5.6.2.6: Relationship with Intestinal Behaviour

The association between intestinal penetrating behaviour (B3) and perianal fistulising disease in this study, independent of other predictors was in keeping with the literature. Some studies have shown that there was no association between the two, prompting their separation within the current Montreal classification.[18, 153] Conversely, other studies have demonstrated that the presence of perianal fistulising disease increased the risk of spontaneous intestinal perforation, especially when colonic disease was present.[154, 155]

5.6.2.7: Association with Extra-Intestinal Manifestations

The increased frequency of extra-intestinal manifestations in children with perianal disease was in keeping with a previous study by Rankin et al.[452] It was not surprising that there was an association between perianal disease and mouth ulcers, independent of orofacial disease, reflecting an overall predilection for inflammation of the squamous epithelium.

The association between perianal disease and dermatological extra-intestinal manifestations and the inverse relationship with hepatobiliary disease has not been reported previously. Reduced risk of hepatobiliary disease at presentation was independent of disease distribution and behaviour, indicating that they may represent two distinct phenotypes of disease.

5.6.2.8: Reduced Frequency of Perianal Disease in p-ANCA positive Children

There was a significantly lower frequency of perianal disease in those who were p-ANCA positive. It could be hypothesized that such children were more likely to have isolated colonic disease (L2), predisposing to inflammatory (B1) instead of fistulising behaviour (B3) and protecting against perianal disease. On logistic regression analysis with these factors included as independent predictors, the presence of p-ANCA remained inversely associated with the presence of perianal disease (OR: 0.36; 95% CI: 0.19, 0.69; p=0.002). Therefore, such children have an UC like disease behaviour.[250]

5.6.3: Conclusion

The presence of perianal lesions in CD added to the heterogeneity of this disease process. There was a clear difference between anal tags/fissures and perianal fistula/abscesses in their associations reflecting a possible difference in pathophysiology. Anal tags and fissures were strongly associated with orofacial lesions, oesophageal disease and dermatological extra-intestinal manifestations, whereas perianal fistula/abscesses were associated with rectal involvement and intestinal perforating behaviour. Therefore, the presence and type of perianal lesions provided a strong and significant association in the CD phenotype.

5.7: Extra-Intestinal Manifestations in IBD

5.7.1: Analysis of Extra-Intestinal Manifestations

Extra-intestinal manifestations were reported in 35.3% (719/2038) of children. The frequencies of various extra-intestinal manifestations by disease subtype are presented in table 5.7.1. There was a significantly higher frequency of extra-intestinal manifestations in CD with 41.2% of children compared to 26.3% in UC (p <0.0001) and 27.5% in IBDU (p <0.0001). In CD, there was a significantly greater proportion of females with extra-intestinal manifestations (46.7%) compared to males (37.4%; p=0.0014).

Table 5.7.1: Extra-intestinal manifestations in children diagnosed with IBD (a child may have more than one manifestation).

EIMs	**CD (n=1211)**	**UC (n=609)**	**IBDU (n=218)**	**IBD (n=2038)**
Hepatobiliary	58[a] (4.8%)	75[a, c] (12.3%)	14[c] (6.4%)	148 (7.2%)
Musculoskeletal	162[a] (13.4%)	43[a] (7.1%)	23 (10.6%)	228 (11.2%)
Ocular	28 (2.3%)	11 (1.8%)	5 (2.3%)	44 (2.2%)
Dermatological	82[a,b] (6.8%)	15[a] (2.5%)	6[b] (2.8%)	103 (5.1%)
Mouth ulcers (aphthous)	289[a,b] (23.9%)	38[a, c] (6.2%)	25[b, c] (11.5%)	352 (17.3%)
Pulmonary	5 (0.4%)	1 (0.2%)	0 (0%)	6 (0.3%)
Other	46 (3.8%)	13 (2.1%)	4 (1.8%)	63 (3.1%)
Total	499 (41.2%)	160 (26.3%)	60 (27.5%)	719 (35.3%)

[a]CD vs UC p<0.05; [b]CD vs IBDU p<0.05; [c]UC vs IBDU p<0.05

5.7.1.1: Hepatobiliary Manifestations

Hepatobiliary manifestations were reported in 7.2% of the children at the time of diagnosis with IBD (table 5.7.1), of which a significantly higher frequency was found in those with UC (12.3%) compared to both CD (4.7%; p <0.0001) and IBDU (6.4%; p=0.0189). The specific hepatobiliary disorder according to disease subtype is shown in table 5.7.2. The majority of the children had elevated liver enzymes with no specific diagnosis followed by sclerosing cholangitis.

5.7.1.1.1: Association between Hepatobiliary EIMs and Phenotype at Diagnosis

In CD, the presence of perianal disease at diagnosis was associated with a lower frequency (chi square analysis p=0.0002) and odds of hepatobiliary disease (OR: 0.29; 95% CI: 0.14, 0.6; p=0.0009). When analysed according to anatomical extent, children with colonic disease (L2/L3) had an increased frequency of hepatobiliary disease (5.2% vs 0.9%; p=0.06). In children with CD, the frequency of p-ANCA positivity was significantly increased in those with hepatobiliary disease compared to those without (62.5% vs 16%; p<0.0001) and even when controlling for disease extent, behaviour, diagnostic age and gender on regression modelling (OR: 8.6; 95% CI: 3.6, 21.7; p<0.0001).

Presence of extensive colitis (E3) in UC was significantly associated with an increased frequency of hepatobiliary disease (14.8% vs 6% in those with left sided colitis or proctitis; OR 2.7; 95% CI: 1.4, 5.5; p=0.0037). In addition, there was a higher frequency of hepatobiliary disease in males compared to females (14.6% vs 9.4%; p=0.072). On regression modelling for the presence of hepatobiliary manifestation with disease extent, age at diagnosis, gender and p-ANCA positivity, the only significant factor was being male (OR: 3; 95% CI: 1.4, 6.4; p=0.0056).

5.7.1.1.2: Sclerosing Cholangitis

There were 38 children diagnosed with sclerosing cholangitis, and it was associated more often with UC (4.1%) compared to CD (1%; p <0.0001). The frequency of p-ANCA positivity was significantly greater in those with sclerosing cholangitis compared to the rest of the cohort (93.3% vs 35.5%; p<0.0001), and this significant association was maintained in both CD (83.3% vs 18.1%; p=0.001) and UC (100% vs 58.5%; p=0.012). In UC, the presence of sclerosing cholangitis was significantly associated with musculoskeletal manifestations (p=0.025).

Table 5.7.2: Number of children with each type of hepatobiliary disorder (a child may have more than one disease manifestation).

	CD	UC	IBDU	IBD
Sclerosing cholangitis	12	25	1	38
Pericholangitis	2	5	2	9
Chronic active hepatitis	1	4	2	7
Autoimmune hepatitis	2	3	0	5
Overlap syndrome (features of autoimmune hepatitis/sclerosing cholangitis)	1	0	0	1
Fatty liver	1	1	1	3
Choleliathiasis	0	0	1	1
Elevated liver enzymes without a specific diagnosis	39	37	8	84
Total	58	75	15	148

5.7.1.2: Musculoskeletal Manifestations in IBD

Musculoskeletal manifestations were reported in 11.2% of the paediatric IBD cohort (table 5.7.1) with a significantly greater frequency in CD (13.4%) compared to UC (7.1%; p <0.0001). Detail on the type of musculoskeletal manifestations is presented in table 5.7.3. More children with CD presented with arthralgia compared to UC (9.2% vs 5.1%; p=0.0025) but there was no significant differences with regard to arthritis. The presence of ocular disease (OR: 4.8; 95% CI: 2.5, 9; p<0.0001), skin lesions (OR: 3.2; 95% CI: 2, 5.1; p<0.0001) and mouth ulcers (OR: 2.3; 95% CI: 1.7, 3.2; p<0.0001) was associated with musculoskeletal manifestations in IBD.

5.7.1.2.1: Association between Musculoskeletal Manifestations and Phenotype at Diagnosis

In CD, the frequency of musculoskeletal manifestations was significantly greater in females (16%) compared to males (11.5%; p=0.029), even when correcting for diagnostic age, anatomical extent and disease behaviour on regression analysis (p=0.026). The presence of musculoskeletal manifestations at diagnosis was significantly increased in those children with dermatological manifestations (24.4% vs 12.6%; OR: 2.2, 95% CI: 1.3, 3.8; p=0.004), ocular disease (42.9% vs 12.7%; OR: 5.2, 95% CI: 2.3, 11.2; p=0.0001) and mouth ulcers (19.7% vs 11.4%; OR: 1.9, 95% CI: 1.3, 2.7; p=0.0004).

With regard to UC, the frequency of musculoskeletal manifestations was significantly increased in those with dermatological manifestations (40% vs 6.2%; OR: 9.9, 95% CI: 3.1, 29.8; p=0.0003) and mouth ulcers (15.8% vs 6.5%; OR: 2.7, 95% CI: 1, 6.6, p=0.043).

Table 5.7.3: Number of children with musculoskeletal EIMs (a child may have more than one manifestation).

	CD	**UC**	**IBDU**	**IBD**
Arthralgia	114 (69%)	31 (73.8%)	15 (65.2%)	157 (68.3%)
Arthritis	44 (26.7%)	11 (26.2%)	7 (30.4%)	62 (27%)
Spondylitis	5 (3%)	0	1 (4.3%)	6 (2.6%)
Enthesitis	1 (0.61%)	0	0	1 (0.4%)
Other	4 (2.4%)	0	0	4 (1.7%)
Total	165	42	23	230

5.7.1.3: Ocular Extra-Intestinal Manifestation

Ocular extra-intestinal manifestations were reported in 2.2% of children diagnosed with IBD, with a similar frequency among CD, UC and IBDU (table 5.7.1). The breakdown of the various eye disorders are presented in table 5.7.4. There was a significantly increased frequency of ocular manifestations in children with IBD when musculoskeletal (OR: 4.8; 95% CI: 2.5, 9; p<0.0001), dermatological (OR: 6.2; 95% CI: 2.8, 12.7; p<0.0001) and mouth ulcers (OR: 3.1; 95% CI: 1.6, 5.8; p=0.0003) were present on both chi square and logistic regression analysis (figure 5.7.1).

5.7.1.3.1: Association between Ocular EIMs and Disease Phenotype

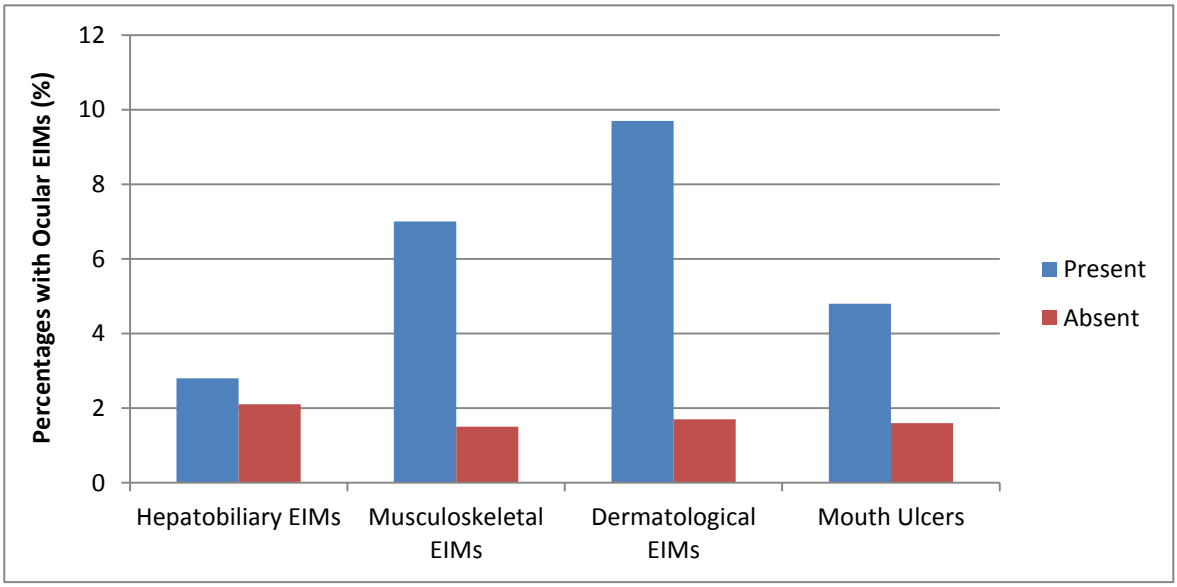
In CD, ocular manifestation was present at diagnosis in a significantly greater frequency of females compared to males (3.6 vs 1.4%; p=0.0205). In addition, the presence of orofacial disease (OR: 4.6; 95% CI: 1.8, 10.5; p=0.0016), musculoskeletal disease (OR: 5.2; 95% CI: 2.3, 11.2; p=0.0001), dermatological manifestations (OR: 6; 95% CI: 2.4, 13.8; p=0.0003) and mouth ulcers (OR: 4.4; 95% CI: 2.1, 9.7; p<0.0001) was associated with ocular changes.

In UC, all of the 11 children with ocular manifestations had extensive colitis (E3; p=0.0222). Among the other extra-intestinal manifestations, it was only the presence of dermatological manifestations associated with ocular disease (OR: 11.1; 95% CI: 1.5, 54.1; p=0.02).

Table 5.7.4: Number of children with eye disorders in IBD (a child may have more than one manifestation).

	CD	UC	IBDU	IBD
Red eye (unspecified)	5 (17.9%)	4 (36.4%)	3 (60%)	12 (27.3%)
Painful eye (unspecified)	4 (14.3%)	1 (9.1%)	1 (20%)	6 (13.6%)
Uveitis	4 (14.3%)	1 (9.1%)	1 (20%)	6 (13.6%)
Conjunctivitis	4 (14.3%)	0	0	4 (9.1%)
Episcleritis	2 (7.1%)	0	0	2 (4.5%)
Iritis	2 (7.1%)	0	0	2 (4.5%)
Unspecified disorder of the eye	7 (25%)	5 (45.5%)	0	6 (13.6%)
Total	28	11	5	44

Figure 5.7.1: Frequency of ocular disease in the presence of other extra-intestinal manifestations in children with IBD.



5.7.1.4: Dermatological Extra-Intestinal Manifestations

Dermatological manifestations were reported in 5.1% of children with IBD in the APAIBD database, 6.8% of those with CD, significantly greater than the 2.5% in UC (p=0.0002) and

2.8% in IBDU (p=0.0341; table 5.7.1). The range of dermatological manifestations is presented in table 5.7.5. The most common lesion was erythema nodosum (2.1%) followed by vasculitic lesions (0.4%) and pyoderma gangrenosum (0.4%) of children with IBD. The presence of musculoskeletal manifestations (OR 3.23; 95% CI: 2, 5.1; p<0.0001), ocular disease (OR: 6.2; 95% CI: 2.8, 12.7; p<0.0001) and mouth ulcers (OR: 3; 95% CI: 2, 4.6; p<0.0001) were associated with dermatological lesions in IBD.

5.7.1.4.1: Association with Disease Phenotype

In CD, dermatological manifestations were significantly associated with orofacial CD (OR 2.7; 95% CI: 1.5, 4.8; p=0.001) and perianal disease (OR: 2.4; 95% CI: 1.5, 4; p=0.0004) with no confounding factors on logistic regression modelling. In addition, dermatological manifestations in CD was associated with the presence of musculoskeletal manifestations (OR: 2.2; 95% CI: 1.3, 3.8; p=0.004), ocular disease (OR: 6; 95% CI: 2.4, 13.8; p=0.0003) and mouth ulcers (OR: 2.7; 95% CI: 1.7, 4.3; p<0.0001). On logistic regression, the presence of mouth ulcers (p=0.037), ocular (p=0.01) and perianal disease (p=0.002) remained as independent predictors for dermatological manifestations at diagnosis.

With regard to UC, there were no phenotypic features at diagnosis associated with increased frequency of dermatological manifestations. Skin lesions were associated with both musculoskeletal involvement (OR: 9.9; 95% CI: 3.1, 29.8; p=0.0003) and ocular disease (OR: 11.1; 95% CI: 1.5, 54.1; p=0.0228) on both chi square analysis and logistic regression.

5.7.1.4.2: Erythema Nodosum in Crohn's Disease

There was a significantly higher frequency of erythema nodosum in children with CD (3.4% vs 0.1% in UC/IBDU; p<0.0001). Erythema nodosum was present in a significantly greater frequency of girls with CD compared to boys (5.4% vs 1.9%; p=0.001). Furthermore, the presence of erythema nodosum was associated with perianal disease (OR: 2.8; 95% CI: 1.4, 5.8; p=0.003) and mouth ulcers (OR: 2.2; 95% CI: 1.2, 4.2; p=0.017). On logistic regression with the above factors and orofacial disease, the presence of perianal disease (p=0.0037) and female gender (p=0.0008) were independently associated with erythema nodosum at diagnosis.

Table 5.7.5: Number of children with dermatological lesions (a child may have more than one lesion).

	CD	UC	IBDU	IBD
Erythema nodosum	42 (51.2)	0	1 (16.7%)	43 (41.7%)
Erythema marginatum	0	1 (6.7%)	0	1 (1%)
Pyoderma gangrenosum	7 (8.5%)	1 (6.7%)	0	8 (7.8%)
Sweet syndrome	0	1 (6.7%)	0	1 (1%)
Vasculitis	6 (7.3%)	2 (13.3)	1 (16.7%)	9 (8.7%)
Other	27 (34.1%)	10 (66.6%)	4 (66.7%)	34 (33%)
Total	82	15	6	103

5.7.1.5: Aphthous Ulcers of the Mouth

Mouth ulcers were present in 17.3% of children with IBD at diagnosis (table 5.7.1). Nearly a quarter of children with CD (23.9%) presented with mouth ulcers which was significantly greater than 6.2% in UC ($p < 0.0001$) and 11.5% in IBDU ($p < 0.0001$). Mouth ulcers were independently associated with the presence of musculoskeletal manifestations (OR: 2.3; 95% CI: 1.7, 3.2; $p<0.0001$), ocular disease (OR: 3.1; 95% CI: 1.6, 5.8; $p=0.0003$) and skin lesions (OR: 3; 95%CI: 2, 4.6; $p<0.0001$) in children with IBD on both chi square analysis and logistic regression.

5.7.1.5.1: Associations with Disease Phenotype at Diagnosis

Mouth ulcers in CD was associated with perianal disease (OR: 2.2; 95% CI: 1.7, 2.9; $p < 0.0001$), musculoskeletal disease (OR: 1.9; 95% CI: 1.3, 2.7; $p=0.0004$), ocular involvement (OR: 4.4; 95% CI: 2.1, 9.7; $p<0.0001$) and skin lesions (OR: 2.7; 95% CI: 1.7, 4.3; $p<0.0001$) on both chi square analysis and logistic regression. The frequency of mouth ulcers in females was significantly greater than males (26.9% vs 21.8%; $p=0.05$) but this was not an independent predictor in a logistic regression analysis. There were no phenotypic associations in UC.

5.7.2: Discussion of Extra-Intestinal Manifestations

5.7.2.1: Frequency of Extra-Intestinal Manifestations

Over a third of children reported in the APAIBD database (719/2038; 35.3%) presented with at least one extra-intestinal manifestation at the time of diagnosis. This was in keeping with other adult and paediatric studies from other parts of the world with reported extra-intestinal manifestation frequency ranging from 6 to 47%.[90, 173-179] It was difficult to compare the overall frequency of extra-intestinal manifestations with other studies because various authors have differing definitions. Some papers defined weight loss and anaemia as an extra-intestinal manifestation which will increase the reported frequency. This was not the case in the APAIBD database where a more stringent definition of extra-intestinal manifestation was applied in data collection.

Within the Australian paediatric IBD cohort, there was a significantly greater frequency of extra-intestinal manifestations in CD. Gender differences was only seen in CD, where significantly more females presented with extra-intestinal manifestations compared to males (46.7% vs 37.4%; p=0.0014). Similar results have been demonstrated in some adult studies with regard to either overall or specific extra-intestinal manifestations, but not in other paediatric studies to date.[124, 173, 174, 179, 453-455]

5.7.2.2: Hepatobiliary Extra-Intestinal Manifestations

The frequency of hepatobiliary extra-intestinal manifestations at diagnosis was in keeping with previous reported rates from other countries ranging from 1 to 8%.[21, 25, 70, 76, 123, 134, 173, 183] Most of the children had elevated liver enzymes with no clear diagnosis, which was not surprising given that information was collected at diagnosis and subsequent hepatobiliary diagnosis was not always recorded.

Children with p-ANCA positive CD had a significantly increased frequency of hepatobiliary manifestations, also increased frequency of sclerosing cholangitis. It was interesting to note that those with colonic involvement (L2/L3) in CD were at increased risk, but had not reached significance probably given the small cohort (n=58). The presence of sclerosing cholangitis in CD may define a unique phenotype consisting of p-ANCA positive colonic disease (L2/L3).[456]

There was a significantly higher frequency of hepatobiliary manifestations and in particular sclerosing cholangitis in children with UC compared to CD and IBDU. Male children and those with extensive colitis (E3) were at greater risk of hepatobiliary manifestations in the UC population. Association with male gender and extensive extent of colitis was not found in sclerosing cholangitis, probably related to the small cohort of 25 children. Similarly, previous studies have reported the presence of UC with primary sclerosing cholangitis was associated with mild extensive disease and male predominance.[176, 179, 457, 458]

As previously described consistently in the literature, p-ANCA positive serology was associated with sclerosing cholangitis in both CD and UC. Thus, such children need to be monitored closely over the long-term for colorectal neoplasia and cirrhosis.[456, 459-461]

5.7.2.3: Musculoskeletal Extra-Intestinal Manifestations

The majority of children had arthralgia (table 5.7.3) followed by arthritis. The frequency of musculoskeletal manifestations was significantly greater in CD, in keeping with other studies.[174, 462] There was a significantly greater frequency of joint involvement in females with CD, also reported by two studies of peripheral arthritis in adults with IBD.[185, 462]

This analysis has reconfirmed the previously demonstrated associations between musculoskeletal extra-intestinal manifestations and skin involvement, ocular disease and mouth ulcers in CD and, skin lesions and mouth ulcers in UC.[185, 187, 462, 463] In the study by Orchard et al,[185] females with either CD or UC were more likely to have pauciarticular (type 1) and polyarticular (type 2) arthritis. Furthermore, there was an association between type 1 arthritis and erythema nodosum and uveitis, and between type 2 arthritis and uveitis.[185]

5.7.2.4: Ophthalmological Extra-Intestinal Manifestations

The eye involvement at diagnosis was predominantly red or painful eyes with no specific diagnosis (table 5.7.4). It was unclear whether these children had an ophthalmology review and what was their subsequent diagnosis. Had follow-up information been collected then these two descriptive categories would have been smaller. Given that there were a small number of children with uveitis, iritis, episcleritis and conjunctivitis, further analysis to explore phenotypic associations was not possible.

Despite the above limitations, the presence of eye lesions in children with CD was associated with orofacial disease, musculoskeletal and dermatological manifestations. This was in keeping with previous studies of similar associations, except for orofacial disease which has not been previously described.[176, 185, 187, 462, 463] The increased frequency in females with CD was interesting and has not been previously reported. There were 3.6% of females presenting with ocular changes compared to 1.4% of males and despite the small proportional difference, it was still significant (p=0.021). This association needs to be monitored over time as the number of children in the database accumulates. Further, a lower threshold for assessment of ocular involvement, perhaps routine eye examination by an ophthalmologist would be appropriate, particularly in females with CD.

In children with UC, the association between ocular manifestations and skin lesions was present. What was interesting was the fact that all of the children with UC and eye disease had extensive colitis (E3). The study by Dotson et al[179] demonstrated that children with pancolitis were more likely to experience an extra-intestinal manifestation than those with rectosigmoid disease.

5.7.2.5: Dermatological Manifestations

Children with CD presented with an increased frequency of skin lesions at diagnosis compared to those with UC or IBDU. Furthermore, erythema nodosum was the most common skin lesion (2.1% of the IBD cohort).

In describing the phenotypic association in CD, it was interesting to note that skin lesions were associated with mouth ulcers, ocular and perianal disease. The question asked was whether these associations were due to erythema nodosum. On further analysis, erythema nodosum was found more often in girls and associated with perianal disease on logistic regression modelling. Similarly, previous studies have demonstrated that erythema nodosum was present more often in CD and among females, and associated with ocular and joint manifestations.[176, 179, 180, 187, 464]

5.7.2.6: Mouth Ulcers

Aphthous ulcers of the mouth were found in a quarter of children with CD at diagnosis, which was greater than the other disease subtypes. In CD, mouth ulcers were associated with orofacial disease, various extra-intestinal manifestations, except for hepatobiliary disease.

The presence of aphthous ulcers and a variety of other lesions in the mouth (orofacial CD) was not surprising given the inflammation within the oral cavity. The association between mouth ulcers and, orofacial and perianal disease probably reflects a unique predilection for inflammation of the squamous epithelium. The study by Lindsley and Schaller[463] demonstrated an association between peripheral arthritis, dermatological lesions and mouth ulcers.

5.7.3: Conclusion

Within the Australian paediatric cohort, the presence of extra-intestinal manifestations at diagnosis with its associations has been described. Given the heterogeneity of the various manifestations and the small population size of individual lesions, further analysis of each manifestation was limited. Ongoing data collection of children with IBD at both diagnosis and follow-up is needed to better describe the various manifestations.

5.8: Anthropometric Parameters at Diagnosis

Within the overall cohort of 2101 children diagnosed with IBD, the weight and height was recorded in 1930 and 1682 children respectively. The number of children with documented weight and height entered into the database was 1161 and 1023 for CD, 569 and 490 for UC, and 200 and 169 for IBDU. Tanner stage was reported in 1393 children (66.3%; table 5.4.1).

5.8.1: Diagnostic Weight (Wt)

Children with CD had a significantly lower median weight z-scores (-0.58; IQR: -1.48, 0.21) compared to UC (-0.09; IQR: -0.82, 0.6; p<0.0001) and IBDU (0.02; IQR: -0.81, 0.73; p<0.0001; table 5.4.2) at diagnosis, which was still significant when controlling for differences in age at diagnosis, gender and symptom duration prior to diagnosis on linear regression modelling. The frequency of weight failure (z-score < -2) was 11.5% in the total IBD cohort and, there was a significantly greater frequency among children with CD (14.9%) compared to UC (6.2%; p <0.0001) and IBDU (6.5%; p=0.002).

5.8.1.1: Crohn's disease

The median z-scores for weight were lower in older children (p=0.0001) and those diagnosed following a longer duration of symptoms (p=0.0001). Other negative influences upon the median weight z-scores at diagnosis included upper gastrointestinal disease involvement (L4±L1/L2/L3), perianal disease, stricturing behaviour (B2) and pre/early puberty (Tanner stage 1 or 2; table 5.8.1). Within the upper gastrointestinal tract, disease involvement of the jejunum was associated with decreased weight (p=0.038). The above factors remained positive even when analysed in a linear regression model with potential confounders.

Children who were ASCA IgA positive at diagnosis had significantly poorer weight (median z-score: -1.02; IQR: -2, -0.45) compared to those who were negative (median z-score: -0.42; IQR: -1.3, 0.45; p=0.0005), even when controlling for disease distribution and behaviour on linear regression modelling (F-test: 8.5; p=0.004; correlation coefficient=0.11). There were no significant associations with ASCA IgG.

Children with upper gastrointestinal tract disease (more specifically oesophageal involvement; p=0.021), stricturing disease behaviour (B2 vs B1; p=0.04), perianal disease (p=0.007), pre- or early puberty (tanner stage 1 or 2; p=0.006) and ASCA IgA positivity (p=0.013) presented with a greater frequency of weight failure (z-score < -2). On logistic

regression with anatomical site and disease behaviour, ASCA IgA positivity remained an independent predictor of weight failure (p=0.03).

5.8.1.2: Ulcerative Colitis

The median z-scores for weight in children with UC at diagnosis are presented in table 5.8.2. Children with proctitis presented with a better weight than those with more extensive disease (E2/E3; p=0.044), even when controlling for other possible confounders (age at diagnosis, gender, duration of symptoms prior to diagnosis and tanner staging).

5.8.1.3: Inflammatory Bowel Disease Unclassified

The median weight z-score at diagnosis was 0.1 (IQR: -0.67, 0.79). Children who were pre/early puberty (Tanner stage 1-2) presented with a significantly lower median weight z-score (-0.06; IQR: -0.85, 0.54) compared to children in later puberty (median: 0.36; IQR: -0.15, 0.93; p=0.0233). In addition, children with a positive first degree family history of IBD presented with a lower weight (median: -0.55; IQR: -1.21, 0.15) compared to the others (median: 0.06; IQR: -0.73, 0.75; p=0.0138).

Table 5.8.1: Median anthropometric parameters at diagnosis in children with CD according to phenotypic features.

	Wt z-score (IQR)	**Ht z-score (IQR)**	**BMI z-score (IQR)**
Overall CD cohort	-0.58 (-1.48, 0.21)	-0.33 (-1.11, 0.41)	-0.65 (-1.62, 0.16)
Gender			
Females	-0.46 (-1.44, 0.26)	-0.27 (-1.05, 0.45)	-0.58 (-1.58, 0.28)
Males	-0.68 (-1.52, 0.21)	-0.39 (-1.13, 0.39)	-0.69 (-1.64, 0.07)
Tanner stage			
1-2 (pre- or early puberty)	-0.77[a] (-1.64, 0.1)	-0.41[f] (-1.2, 0.31)	-0.73[i] (-1.72, 0.08)
3-5	-0.23[a] (-1.03, 0.4)	0.01[f] (-0.83, 0.67)	-0.59[i] (-1.37, 0.26)
Orofacial disease			
Present	-0.32[c] (-1.03, 0.46)	-0.25 (-0.88, 0.30)	-0.40[l] (-1.15, 0.50)
Absent	-0.6[c] (-1.5, 0.2)	-0.33 (-1.12, 0.42)	-0.69[l] (-1.62, 0.12)
Upper Gastrointestinal tract involvement (L4)			
Present	-0.64[b] (-1.61, 0.14)	-0.36[g] (-1.12, 0.38)	-0.82[k] (-1.72, 0.02)
Absent	-0.29[b] (-1.15, 0.55)	-0.21[g] (-0.96, 0.65)	-0.30[k] (-1.18, 0.39)
Lower Gastrointestinal involvement			
Isolated ileal disease (L1)	-0.6 (-1.48, 0.26)	-0.47 (-1.03, 0.27)	-0.67 (-1.64, -0.08)
Isolated colonic disease (L2)	-0.49 (-1.36, 0.28)	-0.27 (-1.16, 0.40)	-0.47[j] (-1.47, 0.26)
Ileocolonic disease (L3)	-0.64 (-1.52, 0.16)	-0.36 (-1.05, 0.43)	-0.80[j] (-1.67, 0.08)
Perianal disease			
Present	-0.7[d] (-1.73, 0.02)	-0.42[h] (-1.14, 0.26)	-0.81[m] (-1.76, -0.09)
Absent	-0.49[d] (-1.34, 0.39)	-0.24[h] (-1.03, 0.61)	-0.46[m] (-1.46, 0.34)
Disease behaviour			
Inflammatory (B1)	-0.55[e] (-1.42, 0.26	-0.32 (-1.05, 0.44)	-0.62[n] (-1.56, 0.20)
Stricturing (B2)	-1.15[e] (-2.03, -0.58)	-0.67 (-1.46, 0.15)	-1.46[n] (-2.26, -0.35)
Penetrating (B3)	-0.85 (-2.26, 0.39)	-0.17 (-1.19, 0.77)	-1.48 (-2.17, 0.18)

[a]p<0.0001; [b]p=0.0001; [c]p=0.0004; [d]p=0.012 ;[e]p=0.0001; [f]p=0.0003; [g]p=0.033; [h]p=0.008; [j]p=0.0251; [k]p<0.0001; [l]p=0.0114; [m]p<0.0001; [n]p=0.0008.

Table 5.8.2: Anthropometrics of children diagnosed with UC.

	Weight z-scores (IQR)	**Height z-scores (IQR)**	**BMI z-score (IQR)**
Overall cohort	-0.09 (-0.82, 0.60)	-0.02 (-0.68, 0.74)	-0.17 (-0.96, 0.5)
Gender			
Females	-0.07 (-0.72, 0.54)	0 (-0.66, 0.72)	-0.14 (-0.87, 0.50)
Males	-0.13 (-0.95, 0.65)	-0.05 (-0.71, 0.74)	-0.22 (-1.01, 0.50)
Tanner stage			
1-2	-0.19 (-0.95, 0.61)	-0.07 (-0.7, 0.64)	-0.17 (-1.04, 0.54)
3-5	0.06 (-0.63, 0.65)	0.09 (-0.74, 0.74)	-0.02 (-0.67, 0.47)
Disease distribution			
Proctitis (E1)	0.18[a] (-0.4, 1.1)	-0.14 (-0.69, 1.0)	0.32[b] (-0.31, 0.98)
Left sided colitis (E2)	-0.08 (-0.76, 0.54)	-0.04 (-0.63, 0.75)	-0.11 (-0.71, 0.52)
Extensive colitis (E3)	-0.11[a] (-0.87, 0.55)	-0.01 (-0.71, 0.72)	-0.24[b] (-1.04, 0.47)

[a]p=0.047; [b]p=0.01

5.8.2: Diagnostic Height

Children with CD presented with a significantly lower median height z-scores (-0.33; IQR: -1.11, 0.41) as presented in table 5.4.2 compared to UC (-0.02; IQR: -0.68, 0.74; p <0.0001) and IBDU (0.1; IQR: -0.67, 0.79; p <0.0001). Height failure (z-score < -2) was found in 6.8% of the total IBD cohort (115/1679). Children diagnosed with CD were more likely to present with height failure with a frequency of 8.9% compared to UC (4.1%; p 0.0011) and IBDU (2.4%; p 0.0058).

5.8.2.1: Crohn's Disease

The height z-score was found to be lower in older children (p=0.0004), prolonged duration of symptoms prior to diagnosis (p=0.0013), pre/early pubertal stage of development (p=0.0003), upper gastrointestinal disease (L4; p=0.033) and perianal disease (p=0.008; table 5.8.1). The difference in height z-score between those with and without upper gastrointestinal tract disease (L4) was not thought to be clinically relevant. The anatomical site contributing to this

difference was oesophageal disease (median: -0.42; IQR: -1.18, 0.12 vs median: -0.31; IQR: -1.06, 0.47 without oesophageal changes; p=0.026).

Children positive for ASCA IgA were found to have a significantly lower median height z-score at diagnosis (-0.53; IQR: -1.10, 0.10; vs 0.04; IQR: -0.85, 0.80; p=0.01), which was independent of disease distribution and behaviour (F-test: 4.59; p=0.034; correlation coefficient: 0.07).

Children who were pre/early pubertal (Tanner stage 1 or 2) presented with a significantly higher frequency of height failure then those in mid-late puberty (11.3% vs 4.1%; p=0.003). Otherwise, there were no other phenotypic features at diagnosis associated with height failure.

5.8.2.2: Ulcerative Colitis

The height z-scores according to various phenotypic presentations are shown in table 5.8.2. The only significant association was that a longer duration of symptoms prior to diagnosis was associated with a poorer height (co-efficient: -0.004; F-test: 8.35; p=0.004; correlation coefficient: 0.02).

5.8.2.3: Inflammatory Bowel Disease Unclassified

The median height z-score was 0.1 (IQR: -0.67, 0.79). In IBDU, there was a gender difference in height z-scores with females having a significantly lower z-score (-0.3; IQR: -0.8, 0.65) compared to males (0.32; IQR: -0.32, 0.84; p 0.0041).

5.8.3: Diagnostic Body Mass Index (BMI)

Body mass index was calculated in 1010 children with CD, 477 with UC and 164 with IBDU. Children with CD presented with a significantly lower BMI z-score at diagnosis compared to UC and IBDU (table 5.4.2). The frequency of BMI failure (z-score < -2) in the overall IBD cohort was 11.7%, with a significantly greater frequency of 14.8% in those diagnosed with CD compared to UC (7.2%; p <0.0001) and IBDU (6.7%; p=0.0076).

5.8.3.1: Crohn's Disease

In CD, children presented with a significantly lower BMI at diagnosis if there were disease involvement of the terminal ileum (p=0.0198), upper gastrointestinal tract (L4; p<0.001) and perianal area (p<0.0001), and stricturing disease behaviour (B2 vs B1; p=0.0008; table 5.8.1).

Within the upper gastrointestinal tract, disease involvement of the oesophagus (p=0.0006), stomach (p=0.007), jejunum (p=0.0001) and proximal ileum (p<0.0001) were all associated with significantly lower BMI z-score. On linear regression with the various anatomical sites of the upper gastrointestinal tract, terminal ileum and disease behaviour, only proximal ileum CD (p=0.0003) and stricturing behaviour (B2; p=0.014) remained independent predictors of lower BMI z-scores. In addition, BMI was lower in those children who were pre/early pubertal (p=0.0028), older (p=0.00001) and diagnosed following a longer symptomatic period (p=0.0028).

Both positivity for ASCA IgA (p=0.0016) and IgG (p=0.025) was associated with a lower BMI, but on linear regression modelling with disease distribution and behaviour included, only ASCA IgA remained significant (p=0.014).

The frequency of children with BMI failure (z-score < -2) was significantly greater in those with Crohn's disease of the proximal ileum (p=0.0005) and/or jejunum (p=0.041), perianal disease (p=0.005) and stricturing behaviour (B2 vs B1; p=0.014).

5.8.3.2: Ulcerative Colitis

In UC, children with extensive colitis (E3) presented with a worse BMI z-score compared to those with proctitis (E1; table 5.6.2). Otherwise, there were no other significant factors influencing BMI.

5.8.3.3: Inflammatory Bowel Disease Unclassified

The median BMI z-score at diagnosis was -0.04 (IQR: -0.89, 0.58). The only significant association identified at diagnosis was the presence of a family history of IBD in a first degree relative associated with a lower median BMI z-score (-0.59; IQR: -1.57, 0.02; n=19) compared to those without a family history (0.06; IQR: -0.87, 0.66; p=0.014; n=135).

5.8.4: Discussion of Anthropometric Data at Diagnosis

The weight, height and BMI z-scores of Australian children diagnosed with IBD were in keeping with previous studies from other centres (table 5.8.3). Children diagnosed with CD presented with poorer z-scores and greater frequency of anthropometric failure compared to those with UC and IBDU, independent of diagnostic age, gender and duration of symptoms

prior to diagnosis (table 5.4.2). These differences may be related to small intestinal inflammation and resulting malabsorption.

Table 5.8.3: Comparison of the z-scores for weight, height and BMI and frequency of failure between Australian children and other international cohorts diagnosed with CD or UC.[11, 70, 150, 197, 198, 203-206, 208-215]

	Australian children (APAIBD)	**International cohorts**
Crohn's disease		
Weight z-score	-0.58	-1.14 to -0.26
Weight failure (z-score < -2)	14.9%	11-27%
Height z-score	-0.33	-1.11 to -0.28
Height failure (z-score < -2)	8.9%	5.3-19%
BMI z-score	-0.65	-1.37 to -0.66
Ulcerative colitis		
Weight z-score	-0.09	-0.32 to 0.2
Weight failure (z-score < -2)	6.2%	5-11%
Height z-score	-0.02	-0.15 to 0.6
Height failure (z-score < -2)	4.1%	2-5%
BMI z-score	-0.17	-0.2 to 0.025

5.8.4.1: Crohn's Disease

5.8.4.1.1: Impact of Age at Diagnosis

It was surprising that increasing diagnostic age was associated with a lower median weight, height and BMI z-scores at diagnosis, independent of duration of symptoms prior to diagnosis, gender and puberty. The age related differences may be due to the fact that the teenage years are a time of rapid growth where potential impairment may be greater. Furthermore, growth is associated with pubertal development which may occur at different chronological ages. Pubertal delay is usually associated with CD and thus, some children may not grow as quickly as those who are healthy at a similar age.[11, 198, 204, 219]

5.8.4.1.2: Prolonged Delay in Diagnosis associated with worsening Anthropometric Parameters

The duration of symptoms prior to diagnosis had an inverse impact on weight, height and BMI z-scores. Sawczenko et al[70, 211] demonstrated an inverse relationship between the duration of diagnostic delay and height z-scores in their cohort of children.[70, 211] Similar association was also demonstrated by Spray et al[206] with regard to height. This may be explained by the fact that such children have malabsorption and thus the longer their disease remained untreated, greater the impact upon growth. Unlike this current cohort, symptomatic duration prior to diagnosis only impacted upon height in the other studies, which was odd given that malabsorption should affect all growth parameters.[70, 206, 211] Possible reason for this discrepancy may be that the inflammation in CD impacted upon the growth hormone axis and thus hindered height more so than weight/BMI. CD may have an impact on pubertal progression, so reporting height z-scores according to chronological age may provide an erroneously low value whereas if corrected for bone age then there may not be any significant differences.[191, 465]

5.8.4.1.3: Impact of Pubertal Stage upon Anthropometric Data

It was not surprising that children who were pre-pubertal (Tanner stage 1) or had started pubertal development (Tanner stage 2) were significantly more likely to have impairments in weight, height and BMI. Inflammation during this period will certainly delay the onset of their accelerated growth and sexual maturation, and subsequently impact the magnitude and duration of growth. On the other hand, teenagers with onset of disease during the later stages of puberty have hopefully already grown and sexually matured.

5.8.4.1.4: Impact of Anatomical Site of Disease

This study highlighted the impairment of growth when there was disease involvement of the jejunum and ileum, with the consequences of malabsorption. Sawczenko et al[70] demonstrated that children with jejunal CD had impairment in both weight and height z-scores whereas disease of the ileum contributed to worsened height at diagnosis. Also, the study by Wine et al[214] demonstrated that ileal disease was associated with height z-scores below -1. The association between oesophageal disease and poorer height at diagnosis reported by Sawczenko et al,[70] was also demonstrated in this study but the magnitude of the difference was not clinically relevant.

5.8.4.1.5: Stricturing Disease Behaviour (B2) contributed to Worsened Nutrition

Similar to the study by Vasseur et al,[210] stricturing disease at diagnosis was associated with significantly lower weight and BMI z-scores. This association was independent of duration of diagnostic delay and anatomical disease involvement of the jejunum and ileum. This was probably due to the lack of nutrition reaching the distal small intestine and impaired absorption. In addition, intestinal strictures at diagnosis may reflect a more aggressive disease process.

5.8.4.1.6: Association between Perianal Disease and Poorer Anthropometric Parameters

It was interesting to demonstrate the association of perianal disease with weight, height and BMI z-scores. Even when controlling for other phenotypic features associated with perianal lesions in a linear regression analysis, perianal disease remained an independent predictor. This has not been previously described in the literature. Possible pathophysiological explanation is uncertain, except that the presence of perianal disease may reflect a more severe disease process and its presence may be associated with decreased oral intake given the perianal pain.

5.8.4.1.7: ASCA IgA positivity predicted Worsened Anthropometric Parameters at Diagnosis

In this study, ASCA IgA positivity was associated with a significantly poorer weight, height and BMI z-score at diagnosis, which was independent of small bowel disease and complicating disease behaviour (B2/B3). Similar results were demonstrated by Trauernicht et al,[215] in which children with ASCA IgA positivity had significantly lower weight and height z-scores at diagnosis, independent of disease location. In addition, ASCA IgG positivity and the titre of antibody were associated with poorer weight, but disease behaviour was not included in their analysis.[215] The association between ASCA positivity and poorer anthropometric parameters may be related to a distinctive type of inflammation triggered by the bacterial flora within the bowel, not fully explained by small intestinal involvement and stricturing/penetrating behaviour.[229, 237, 249, 318, 466, 467]

5.8.4.1.8: Lack of Gender Differences

Within the Australian cohort, there were no gender differences in weight, height and BMI z-scores at diagnosis. In contrast, both the study from Great Britain/Ireland[70] and Northern

France[210] demonstrated that girls presented with a significantly lower weight compared to boys.

5.8.4.2: Ulcerative Colitis

There were two important associations found in children with UC. Children presenting with extensive colitis (E3) were more likely to have poorer weight and BMI z-scores. This has not been reported previously. Despite the fact that UC is considered a mucosal disease, having an extensive colitis may reflect a more severe disease process with associated decreased oral intake and increased metabolic needs.

Duration of symptoms prior to diagnosis had a significant impact on height z-scores but not weight or BMI. This confirmed the findings by Hildebrand et al,[204] who followed the growth of children with IBD from birth to adulthood, and found that there was a decrease in height percentiles within one year prior to diagnosis of UC.

5.8.5: Limitations of Anthropometric Analysis

5.8.5.1: Assessing Anthropometric Parameters according to Bone Age

Children with CD were more likely to have pubertal delay and assessing anthropometric parameters according to chronological age may generate low values, not reflecting the true impact on growth. Therefore, it is important to determine the child's bone age at diagnosis so that an appropriate assessment can be undertaken according to this age, minimising misinterpretation and over aggressive therapy.[465] This discrepancy between chronological and bone age may be greater in older children.[191]

5.8.5.2: Height Velocity may be a Better Measure

Within this study, a single measure of height at diagnosis compared to the normal published range for age and gender (z-score) was used to assess growth. This was fraught with problems as it does not identify those children who had a fall in their growth over the preceding time prior to diagnosis. Furthermore, it does not incorporate the child's ethnicity and their parents' height percentiles, thus not reflecting their growth potential. For example, a child may be small for their age, tracking along 2 standard deviations below the normal range, which would be considered as significant growth impairment. But the child's parents may also have short stature and thus the child is following his or her familial curve. A better measure would be height velocity according to bone age which will identify any slowing in

growth and not be influenced by the above factors except for disease.[468] The limitation is that children usually present with no previous height measurements.

5.8.6: Conclusion

Within this Australian cohort of children, CD had a negative impact upon anthropometrics. Previous relationships with disease phenotype have been reproduced, but also new associations have been identified in this large paediatric population. Given the impact of disease, it is important that tailored therapy is provided to not only suppress the inflammation but also optimise their growth.

5.9: Are there any Regional Variation in Disease Phenotype between the Australian states?

5.9.1: Comparison between the Australian States

The number of children diagnosed among the various states and the phenotypic features at diagnosis are presented in table 5.9.1.

5.9.1.1: Disease Subtype within and between the various States

All the states had a predominance of CD with a frequency of 53-62% (table 5.9.1). Victoria had a significantly greater frequency of CD (62.1% vs 57.5%; p=0.038) and lower frequency of UC (23.7% vs 34.4%; p<0.001) compared to the rest of Australia. There was a significantly greater proportion of UC diagnosed in Queensland (39.3% vs 29.4%; p=0.016), South Australia (41.2% vs 27.7%; p<0.001) and Western Australia (40.9% vs 29.5%; p=0.015) compared to the rest of the country.

5.9.1.2: Gender Differences

The overall cohort demonstrated a predominance of males but Western Australia was the only state where there was a female predominance of children with IBD (55.5% vs 42.9% of the rest of Australia; p=0.013).

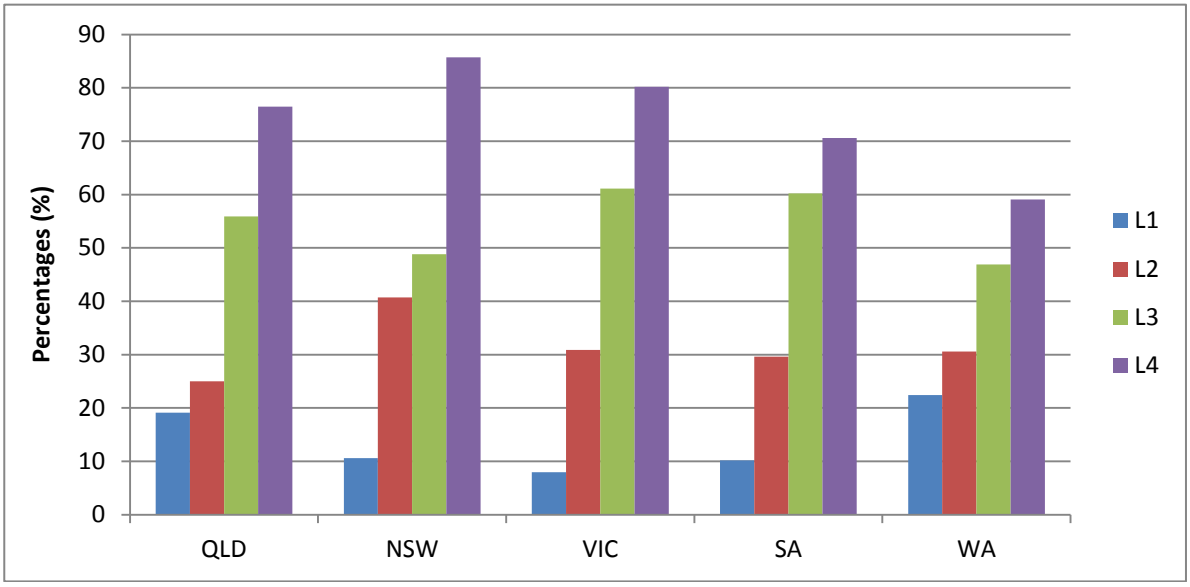
Table 5.9.1: IBD phenotype at diagnosis among the Australian states.

	NSW	VIC	QLD	WA	SA	TAS	ACT	NT
Nos of children	577	847	145	110	364	23	27	5
Disease subtype								
CD	60.8%	62.1%	55.9%	53.6%	53.3%	60.9%	59.3%	80%
UC	28.1%	23.7%	39.3%	40.9%	41.2%	30.4%	29.6%	20%
IBDU	11.1%	14.2%	4.8%	5.5%	5.5%	8.7%	11.1%	
Age at diagnosis (IQR)	11.3yrs (8.4,13.5)	12yrs (9,14)	11.2yrs (8.4,13.2)	11.9yrs (9.1,14.1)	12.6yrs (10,14.8)	10.2yrs (6.9,12)	11.6yrs (4.5,14.8)	14.2yrs (13.7,15.9)
Duration of symptoms prior to diagnosis (IQR)	24.5wks (11,54)	17wks (8.5,54)	20.5wks (11,52)	20.5wks (10,32)	13.5wks (6,29)	24wks (10.5,46)	37wks (8,52)	30wks (25.5,75)
Gender (males)	53.2%	58.7%	55.2%	44.6%	59.6%	69.6%	63%	40%
EIMs	37.7%	33%	37.4%	45.7%	34.4%	21.7%	29.6%	40%
First degree family history of IBD	10.8%	9.9%	7.1%	9.7%	9.3%	0	0	0

5.9.1.3: Gastrointestinal Disease Extent in CD among the States

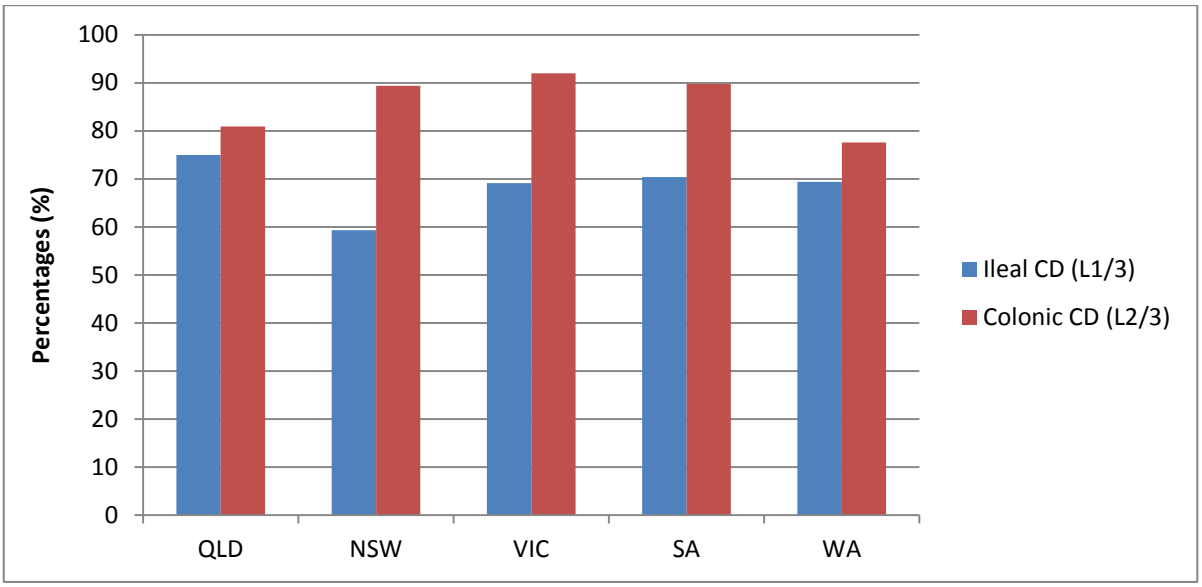
The disease extent in CD is presented in figure 5.9.1 and figure 5.9.2. There was significantly less colonic CD (L2/L3) in Queensland (80.9% vs 90.5%; p=0.019) and Western Australia (77.6% vs 90.5%; p=0.007) compared to the rest of Australia, whilst there was significantly greater colonic CD in Victoria (92% vs 88.3%; p=0.047). On the other hand, there was less ileal CD (L1/L3) in New South Wales (59.3% vs 70%; p<0.001). With regard to disease involvement proximal to the terminal ileum (L4), there was a significantly greater proportion in New South Wales (85.7% vs 76.5%; p=0.002), and significantly less in South Australia (70.6% vs 80.6%; p=0.004) and Western Australia (59.1% vs 79.8%; p=0.0019) compared to the rest of Australia.

Figure 5.9.1: Interstate comparison of gastrointestinal tract disease distribution in CD.



L1: isolated terminal ileum; L2: isolated colonic; L3: ileocolonic; L4: upper gastrointestinal.

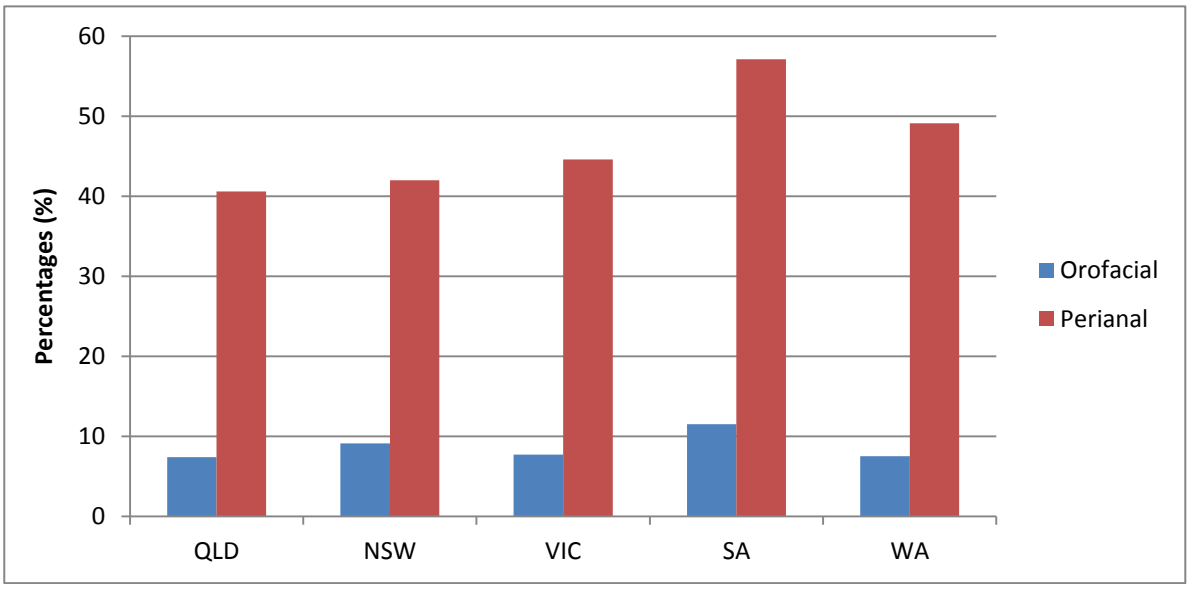
Figure 5.9.2: Distribution of lower gastrointestinal tract disease in children with CD among the various states.



5.9.1.4: Orofacial and Perianal disease in CD among the States

There were no regional differences in the proportion of orofacial disease among the various states (figure 5.9.3). With regard to perianal disease, South Australia had a significantly greater reported frequency of 57.1% at diagnosis compared to 43.9% in the rest of the cohort (p=0.001). Upon stratification according to type of lesion, this significantly increased frequency was found among anal tags (39.9% vs 26.3%; p=0.0002) and fissures (42% vs 28.8%; p=0.0004). There was no significant differences in the frequency of complicated lesions (perianal fistula, abscesses) and ulcers.

Figure 5.9.3: Distribution of orofacial and perianal lesions in children with CD among the states.



5.9.1.5: Disease Behaviour in Crohn's disease between the States

There was a predominance of inflammatory behaviour across Australia. There were no significant differences in the frequency of complicating behaviour (B2/B3) at diagnosis between the states (table 5.9.2).

Table 5.9.2: Distribution of CD behaviour between the various states.

	QLD	NSW	ACT	VIC	TAS	SA	WA	NT	Entire CD cohort
Inflammatory (B1)	63 (91.3%)	314 (92%)	16	489 (94%)	12 (85.8%)	172 (89.1%)	52 (96.3%)	3	1121 (92.6%)
Stricturing (B2)	4 (5.8%)	22 (6.5%)	0	26 (5%)	2	16 (8.3%)	1	1	72 (5.9%)
Penetrating (B3)	2 (2.9%)	5 (1.5%)	0	5 (1%)	0	5 (2.6%)	1	0	18 (1.5%)
Total in each state	69	341	16	520	14	193	54	4	1211

5.9.1.6: Disease Extent in UC

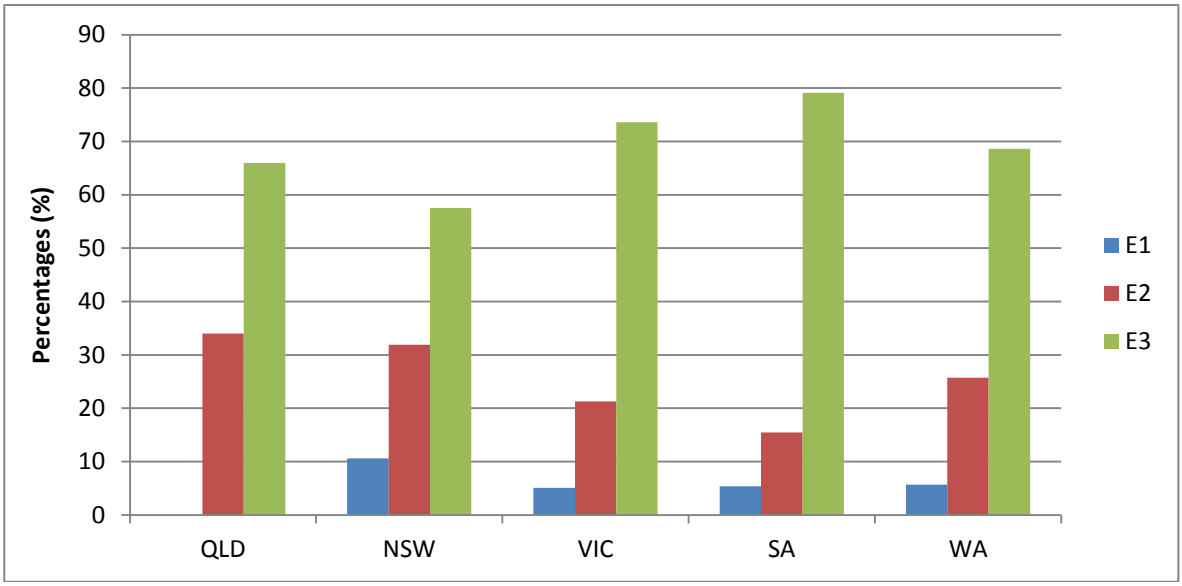
Across Australia there was a predominance of colitis extending beyond the splenic flexure (E3) as shown in table 5.9.3 and figure 5.9.4. New South Wales had a significantly greater proportion of proctitis (E1; 10.6% vs 4.5%; p=0.01) and a decreased proportion of extensive colitis (E3; 57.5% vs 73.9%; p= 0.0002) compared to the rest of Australia (figure 5.9.4).

South Australia had a significantly greater proportion of extensive colitis (79.1% vs 66.5% rest of the cohort; p=0.005).

Table 5.9.3: Extent of colitis in children diagnosed with UC between states.

	QLD	NSW	ACT	VIC	TAS	SA	WA	NT	Entire UC cohort
Proctitis (E1)	0	17 (10.6%)	0	10 (5.1%)	0	8 (5.4%)	2 (5.7%)	0	37 (6.1%)
Left sided colitis (E2)	17 (34%)	51 (31.9%)	3	42 (21.3%)	2	23 (15.5%)	9 (25.7%)	0	147 (24.3%)
Extensive colitis (E3)	33 (66%)	92 (57.5%)	5	145 (73.6%)	4	117 (79.1%)	24 (68.6%)	1	421 (69.6%)
Total of each state	50	160	8	197	6	148	35	1	605

Figure 5.9.4: Extent of colitis in children diagnosed with UC between the various states.



5.9.1.7: Comparison between the Western and Eastern parts of Australia

5.9.1.7.1: Overall IBD cohort

Australia was divided between the west and east so that any differences in disease phenotype can be explored. The Western part consisted of West Australia (WA) and the Eastern part consisted of Queensland (QLD), New South Wales (NSW) and Victoria (VIC). There was a significantly greater proportion of UC diagnosed in Western Australia (table 5.9.4). Fewer males were diagnosed with IBD compared to females in the west (table 5.9.4).

Table 5.9.4: Comparison between Western and Eastern parts of Australia with regard to IBD diagnosis.

	West (WA)	**East (QLD, NSW VIC)**
Number of children diagnosed with IBD	110	1569
Disease subtype		
CD	59[a] (53.6%)	958[a] (61.1%)
UC	45[a,b] (40.9%)	420[a,b] (26.8%)
IBDU	6[b] (5.5%)	191[b] (12.2%)
Age at diagnosis (IQR)	11.9 years (9.1, 14.1)	11.7 years (8.7, 13.7)
Duration of symptoms prior to diagnosis (IQR)	20 weeks (10, 32)	21 weeks (9, 52)
Gender (males)	49[c] (44.5%)	884[c] (56.3%)
Family history of IBD (1st degree)	9 (9.7%)	147 (10%)

[a]p=0.009; [b]p=0.006; [c]p=0.021

5.9.1.7.2: Crohn's Disease

The phenotypic differences between the west and east are presented in table 5.9.5. In Western Australia there was significantly less upper gastrointestinal disease (L4) and less colonic disease (L2/3; p=0.01).

Table 5.9.5: Differences in CD phenotype at diagnosis between the Western and Eastern parts of Australia.

	West (WA)	**East (QLD, NSW, VIC)**
Number of children	59	958
Age at diagnosis (IQR)	11.7 years (9.8, 13.5)	12.1 years (9.4, 14.1)
Duration of symptoms prior to diagnosis (IQR)	25 weeks (12, 47)	24 weeks (12, 52)
Gender (males)	27 (45.8%)	556 (58%)
Family history of IBD (1st degree)	5 (9.8%)	95 (10.4%)
Anatomical disease distribution		
Orofacial disease	4 (7.5%)	76 (8.2%)
Upper Gastrointestinal disease (L4)	26[a] (59.1%)	647[a] (81.9%)
Lower gastrointestinal disease		
Isolated terminal ileal (L1)	11[b,c] (22.4%)	87[b,c] (9.8%)
Isolated colonic (L2)	15[b] (30.6%)	303[b] (34%)
Ileocolonic (L3)	23[c] (46.9%)	501[c] (56.2%)
Perianal disease	26 (49.1%)	393 (43.4%)
CD behaviour		
Inflammatory (B1)	52 (96.3%)	866 (93.1%)
Stricturing (B2)	1 (1.9%)	52 (5.6%)
Penetrating (B3)	1 (1.9%)	12 (1.3%)

[a]p=0.0004; [b]p=0.037; [c]p=0.013

5.9.1.7.3: Ulcerative Colitis

There were no significant differences in the phenotypic features of UC between the Western and Eastern parts of Australia (table 5.9.6).

Table 5.9.6: Comparison of phenotypic features at diagnosis in children with UC between the West and Eastern parts of Australia.

	West (WA)	**East (QLD, NSW, VIC)**
Number of children	45	420
Age at diagnosis (IQR)	11.9 years (7.8, 14.1)	11.3 years (7.3, 13.2)
Duration of symptoms prior to diagnosis (IQR)	16 weeks (6, 24)	14 weeks (8, 36)
Gender (males)	20 (44.4%)	224 (53.3%)
Family history of IBD (1^{st} degree)	3 (7.9%)	33 (8.6%)
Anatomical extent of disease		
Proctitis (E1)	2 (5.7%)	27 (6.6%)
Left sided colitis (E2)	9 (25.7%)	110 (27%)
Extensive colitis (E3)	24 (68.6%)	270 (66.3%)

5.9.1.8: Comparison of Disease Phenotype between the Northern and Southern parts of Australia

5.9.1.8.1: Overall IBD cohort

Australia was divided along the Eastern coast given its large geographical size, concentration of the population on the east coast and more importantly to control for differences between west and east. The Northern part of Australia consisted of Queensland (QLD) whilst the Southern part consisted of Victoria (VIC) and Tasmania (TAS). Within the overall cohort there were no significant differences between the two regions, except for the median age at diagnosis but this was not thought to be clinically relevant given the magnitude of the difference (table 5.9.7).

Table 5.9.7: Characteristics of children diagnosed with IBD between Northern and Southern parts of Australia.

	North (QLD)	**South (VIC/TAS)**
Number of children diagnosed with IBD	145	870
Disease subtype		
CD	81 (55.9%)	540 (62.1%)
UC	57 (39.3%)	208 (23.9%)
IBDU	7 (4.8%)	122 (14%)
Age at diagnosis (IQR)	11.2 yrs[a] (8.4, 13.2)	12 yrs[a] (9, 13.9)
Duration of symptoms prior to diagnosis (IQR)	20.5 wks (10, 52)	17 wks (8, 52)
Gender (males)	80 (55.2%)	513 (59%)
Family history of IBD (1st degree)	9 (7.1%)	79 (9.6%)

[a]p=0.017

5.9.1.8.2: Crohn's Disease

The phenotypic features of children diagnosed with CD are presented in table 5.9.8. Children living in Queensland presented with a significantly greater frequency of isolated terminal ileum disease (L1) than those diagnosed in the Southern states of Australia (table 5.9.8).

Table 5.9.8: Phenotypic features at diagnosis of children with CD between the Northern and Southern parts of Australia.

	North (QLD)	**South (VIC, TAS)**
Number of children	81	540
Age at diagnosis (IQR)	11.8 yrs (9.5, 13.9)	12.2 yrs (9.5, 14.2)
Duration of symptoms prior to diagnosis (IQR)	21 wks (12, 50)	24 wks (10, 52)
Gender (males)	44 (54.3%)	327 (60.6%)
Family history of IBD (1st degree)	5 (6.7%)	51 (10%)
Anatomical disease distribution		
Orofacial disease	5 (7.4%)	43 (8.1%)
Upper Gastrointestinal disease (L4)	26 (76.5%)	396 (80%)
Lower gastrointestinal disease		
Isolated terminal ileal (L1)	13[a,b] (19.1%)	40[a,b] (7.8%)
Isolated colonic (L2)	17[a] (25%)	160[a] (31.1%)
Ileocolonic (L3)	38[b] (55.9%)	315[b] (61.2%)
Perianal disease	26 (40.6%)	237 (44.7%)
CD behaviour		
Inflammatory (B1)	63 (91.3%)	501 (93.8%)
Stricturing (B2)	4 (5.8%)	28 (5.2%)
Penetrating (B3)	2 (2.9%)	5 (0.9%)

[a]p=0.009; [b]p=0.009

5.9.1.8.3: Ulcerative Colitis

There were no differences in phenotypic features of children diagnosed with UC between Queensland and Victoria/Tasmania (table 5.9.9).

Table 5.9.9: Phenotypic features of children diagnosed with UC between the Northern and Southern regions of Australia.

	North (QLD)	**South (VIC, TAS)**
Number of children	57	208
Age at diagnosis (IQR)	10.2 years (4.4, 11.7)	12 years (8.2, 13.6)
Duration of symptoms prior to diagnosis (IQR)	24 weeks (8, 52)	13 weeks (8, 26)
Gender (males)	30 (52.6%)	117 (56.3%)
Family history of IBD (1st degree)	3 (6.4%)	16 (8.2%)
Anatomical extent of disease		
Proctitis (E1)	0	10 (4.9%)
Left sided colitis (E2)	17 (34%)	44 (21.7%)
Extensive colitis (E3)	33 (66%)	149 (73.4%)

5.9.2: Discussion of Regional Differences

5.9.2.1: Differences between the States

There were significant differences in disease phenotype among the various states. Australia is a large country with variation in geographical terrain, population size and climate. Thus, these differences in phenotype may be explained by environmental factors and so further study of these potential influences need to be undertaken.

Given the incomplete data from the various states, except for South Australia, incidence could not be calculated and thus comparisons between the various regions were not possible. Australia is an ideal country for regional analysis because of its large size, differences in terrain, weather, ethnic composition, age distribution, access to health care and various other environmental exposures, including microbiological organisms.

Data from some international studies would suggest a north-south difference in the incidence of CD and UC in both adults and children.[54-57] Interpretation of European studies showed that there was a higher rate of new cases of IBD in children from the northern parts of Europe (table 2.3), with the exception of Northern France, Spain and Croatia.[13, 26, 30, 41] It was interesting to note that this variation was due to CD as suggested by a Scottish study

demonstrating a significantly higher incidence of paediatric CD in the northern parts of Scotland with no differences seen in the incidence of UC.[56] Similar results were found in a French study demonstrating a higher incidence of CD in the north, but no differences in UC, from a combined cohort of children and adults.[57]

5.9.2.2: Better Data Collection

The number of children recorded in the database from most states was not complete, except for South Australia and Victoria. This was one of the limitations of a physician reporting database.[28] With ongoing and complete data from across Australia, comparison can be undertaken to delineate differences in epidemiology and phenotype between regions.

5.9.3: Conclusion

Analysis of this Australian database has revealed some differences between the various states. This was limited by the incomplete data collection from some states, which may have impacted upon interpretation of these differences. Given the large size of Australia, it is of utmost importance that all children diagnosed with IBD are captured, allowing important comparisons to be undertaken between regions and over time.

5.10: Incidence of IBD in South Australia

5.10.1: Analysis of South Australian Data

There were 275 children aged 15 years or younger diagnosed with IBD between the 1st of January 1996 and 31st of December 2009 in South Australia. Of the 275 children, two did not have any recorded post-code of residence. Within this cohort, there was a predominance of CD with 155 children, followed by 99 children with UC and 21 with IBDU. The number of cases over the study period is shown in figure 5.10.1. The details of the children included in the study are presented in table 5.10.1.

Figure 5.10.1: Children diagnosed with IBD in South Australia between 1996 and 2009.

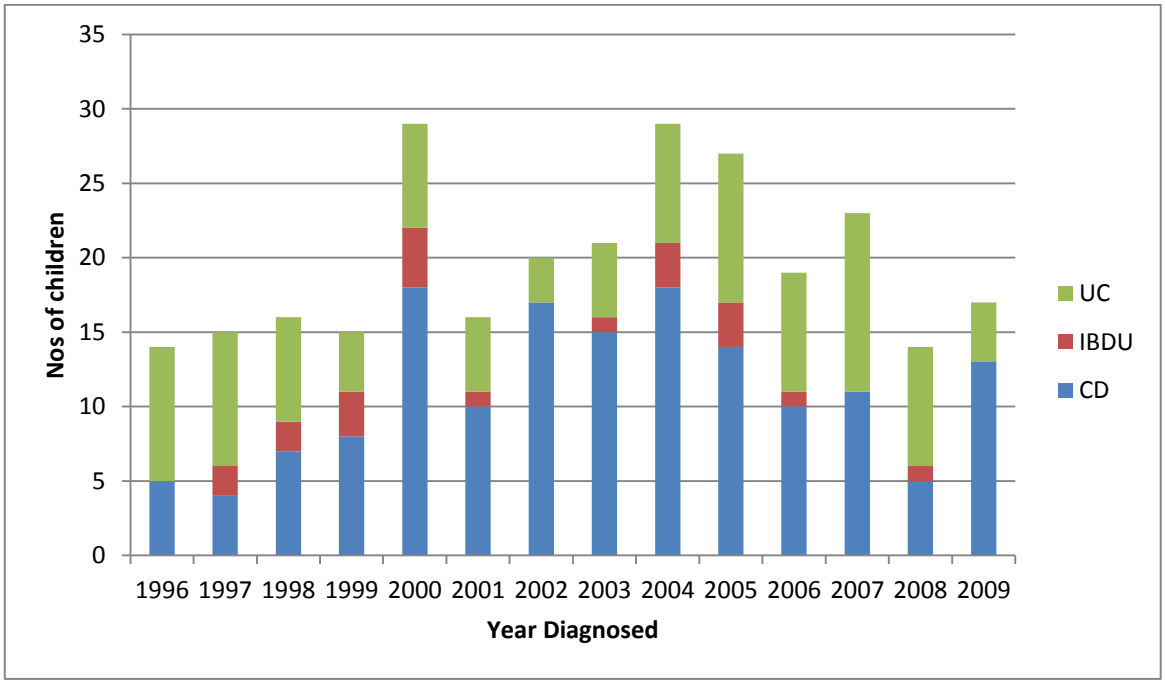


Table 5.10.1: Children diagnosed with IBD in South Australia (1996-2009).

Phenotypic details	**CD (n=155)**	**UC (n=99)**	**IBDU (n=21)**	**IBD (n=275)**
Age at diagnosis (IQR)	12.5yrs (10.5, 14)	12yrs (8.5, 14)	11yrs (10.5, 13)	12.5yrs (10, 14.5)
Gender distribution (male)	100 (64.5%)	52 (52.5%)	12 (57.1%)	166 (60.4%)
Duration of symptoms prior to diagnosis (IQR)	16.5wks (8.5, 32)	8.5wks (5, 20)	13wks (11, 25)	12.5wks (6.5, 26)
EIMs	47.2%	22.4%	20%	35.8%
Wt z-score (IQR)	-0.48 (-1.15, 0.28)	0.01 (-0.78, 0.48)	0.39 (-0.45, 0.71)	-0.22 (-1.06, 0.4)
Ht z-score (IQR)	0.01 (-0.9, 1.22)	0.22 (-0.52, 1.07)	0.49 (-0.5, 1.09)	0.04 (-0.7, 1.18)
BMI z-score (IQR)	-0.29 (-1.42, 0.7)	0.05 (-0.7, 1)	0.53 (-0.57, 1.22)	-0.16 (-0.99, 0.91)

The incidence of IBD, CD, UC and IBDU is shown in figure 5.10.2. The incidence of IBD in South Australia was 6.43 per 100,000 person years over the study period. The incidence of CD was 3.62 and UC was 2.31 per 100,000 person years during 1996-2009. There was no significant change in the incidence of IBD, CD or UC over the study period. There was a linear upward trend in CD (p=0.064) but then this reversed from 2005 onwards. There was a peak in IBD incidence in 2000 and 2004/2005. The incidence figures among the various regions are presented in table 5.10.2. There were no significant differences between the various regions.

Figure 5.10.2: Incidence of IBD in South Australian children (1996-2009).

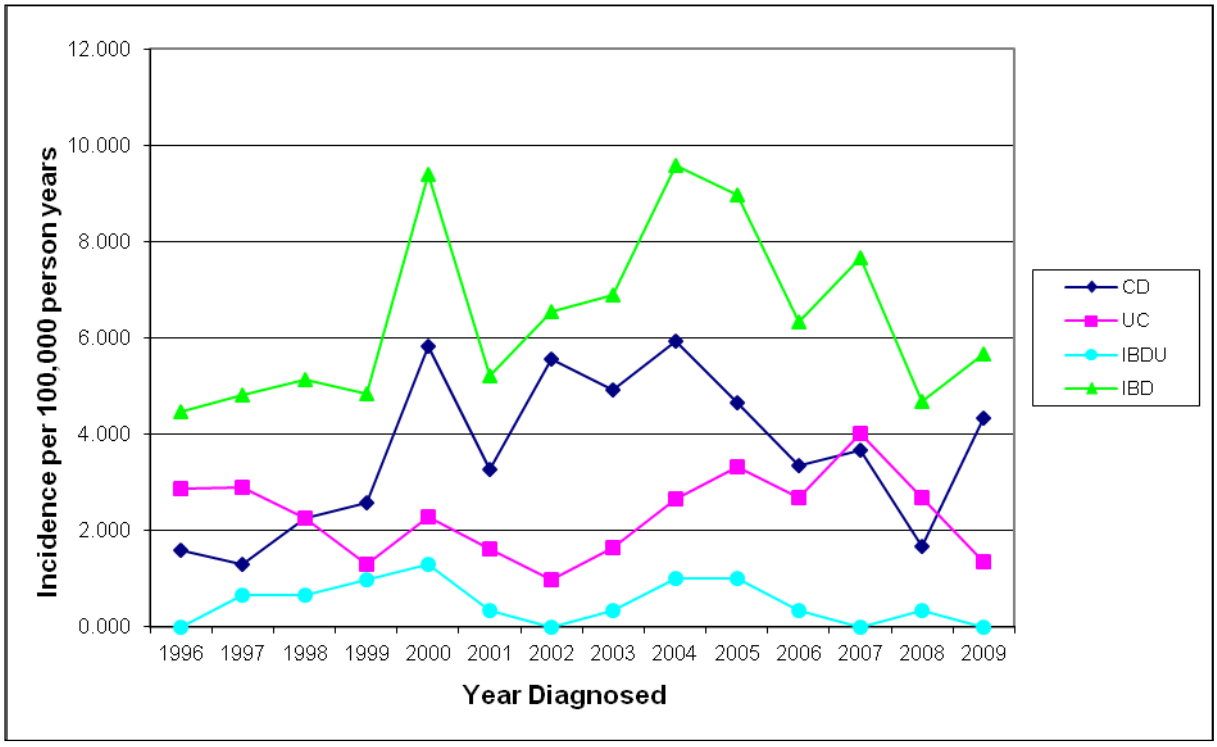


Table 5.10.2: Incidence of IBD among the different regions of South Australia (1996-2009).

Statistical divisions	Number of cases	Incidence per 100,000 person years
Adelaide	204	6.80
Outer Adelaide	27	7.49
Yorke and Lower North	7	5.4
Murray Lands	9	4.23
South East	9	4.47
Eyre	3	2.71
Northern	14	5.36
Entire South Australia	273	6.43

5.10.2: Discussion of South Australian Incidence

5.10.2.1: Comparison of South Australian incidence figures to Other Regions

Within South Australia, the incidence of IBD, CD and UC was higher than that reported in both Victoria and New Zealand (table 5.10.3).[21, 49, 50] Despite the variation in age range and the time period of the studies, this demonstrated a true difference in incidence figures. The incidence figures from South Australia were among the highest reported worldwide with a few exceptions (table 5.10.3).

Table 5.10.3: Incidence figures of children diagnosed with IBD for Australasia compared to other cohorts.

	Year	Age of children	IBD	CD	UC
South Australia, Australia	1996-2009	<16 yrs	6.43	3.62	2.31
Victoria, Australia[21]	1996-2001	<17yrs		2.0	
Victoria, Australia[49]	1990-2009	<17yrs			1.05
New Zealand[50]	2002-2003	<15yrs	2.9	1.9	0.5
EUROPE					
Britain and Ireland[29]	1998-99	<16yrs	5.2	3.1	1.4
Primorsko-Goranska County, Croatia[26, 30]	2000-2004	<15yrs		8.69	0.86
Moravia, Czech Republic[23]	1998-2001	<16yrs	2.24	2.69	1.84
Czech Republic[9]	2001	<15yrs		1.26	
Tampere and Helsinki district, Finland[31]	2003	<18yrs	7.0	2.6	3.2
Finland[32]	2003	<18yrs	15	5	9.1
Northern France[13]	1997-99	<17yrs	3.1	2.6	0.8
Ireland[33]	2000-2010	<16yrs	3.9	2.3	1.1
Italy[34]	2003	<18yrs	1.39		
Netherlands[28]	1999-2001	<18yrs	5.2		
Southeastern Norway[36]	1990-93	<16yrs	4.7	2.7	2.0
Southeastern Norway[37]	1990-94	<16yrs	4.15	2	2.14
Southeastern Norway[38]	1999-2004	<16yrs	5.65	3.64	2.05
Poland[10]	2002-2004	<18yrs	2.7	0.6	1.3
Scotland[39]	1991-95	<17yrs		3.0	1.8
Scotland[40]	2003-2008	<16yrs	7.82	4.75	2.06
Oviedo, Northern Spain[26, 41]	2000-2002	<15yrs		5.76	1.63
Sweden[14]	1993-95	<16yrs	7.0	1.3	3.2
Northern Stockholm, Sweden[22]	1999-2001	<16yrs	10.5	8.4	1.8
South Glamorgan, Wales[43]	1989-93	<16yrs		3.11	0.7
Cardiff/the Vale, South Wales[44]	1983-93	<16yrs	5.4	3.6	1.5
Wales[45]	1995-97	<16yrs	2.6	1.36	0.75
NORTH AMERICA					
Metropolitan Toronto, Canada[6]	1991-96	<18yrs		3.7	2.7
Ontario, Canada[27]	1994-2005	<18yrs	11.4	6	4.2
Wisconsin, USA[25]	2000-2001	<18yrs	7.05	4.56	2.14
ASIA					
Kuwait[46]	1998-2008	<16yrs	2.16	1.53	0.6
Riyadh, Saudia Arabia[47]	1993-2002	<18yrs	0.5		
AFRICA					
Benghazi, Libya[48]	2006	<15yrs	0.91		

Like other regions of the world, there was a greater proportion of CD diagnosed than UC in South Australia (table 5.10.3). This was the case in most of the international cohorts with the exception of Finland[31, 32] and Poland.[10]

5.10.2.2: Temporal Changes in Incidence of IBD

The incidence of IBD has changed over time with mostly increases in CD. Such increasing incidence was reported from Scotland (1968-2008),[39, 40, 58] Czech Republic (1990-2001),[9] Northern Stockholm (Sweden; 1990-2001),[22] Finland (1987-2003)[31, 32] and Victoria, Australia (1971-2001).[21] In the Victorian study, the incidence of CD increased 15-fold between 1971 and 2001.[21] In the current South Australian study there was a trend of increasing incidence of Crohn's disease between 1996 and 2009 ($p=0.064$). Had the study extended to earlier decades then there may have been a significant increase. It was interesting to note that during the same period of this study, there was a smaller increase in the incidence of CD in Victoria from 1991 to 2001.[21]

In contrast, most studies have demonstrated that the incidence of UC in children has remained stable or decreased. Significant increases in UC were reported from Sweden (1984-1995),[14] Scotland (1990-2008),[39, 40, 58] Finland (1987-2003)[31, 32] and Slovenia (1994-2005).[59] In Victoria (Australia) there has been a 11 fold increase from 0.15 (1950) to 1.61 per 10^5 per year (2009), which was significant when comparing the time periods of 1950-1969 (0.3 per 10^5 per year) to 1990-2009 (1.05 per 10^5 per year).[49] In comparison, there was no significant change in the incidence of UC between 1996 and 2009 within South Australia.

5.10.2.3: Regional Variation within the State

There have been inconsistent reports of regional variation between north-south, especially with regard to CD.[42, 54, 55, 57] The Scottish paediatric study by Armitage et al[56] showed a significantly increased incidence of CD in Northern areas, but no difference in UC. This regional variation was not demonstrated in this South Australian cohort.

In Victoria (Australia), there was a significantly greater number of children diagnosed with CD from Melbourne compared to the rural areas.[21] In comparison, there were no differences in incidence between the urban (Adelaide) and rural areas (rest of South Australia).

5.10.2.4: Accuracy of Incidence Figures

South Australia provided an ideal environment for collecting complete data on children diagnosed with IBD. There was only four paediatric gastroenterologists in the state who treated children aged 15 years or younger.

5.10.3: Conclusion

The incidence of IBD among South Australian children during 1996 to 2009 has remained stable, but higher than that reported from Victoria. The lack of temporal change is probably related to the short time period and relatively small paediatric population compared to other studies. Ongoing data collection may highlight variation in incidence within this state and among the various regions.

5.11: Concluding Remarks on Disease Phenotype at Diagnosis

This study demonstrated that Australian children diagnosed with IBD presented with similar phenotypic features to those described in other international studies. Utilising this large database, age related changes in disease extent, intestinal disease behaviour, extra-intestinal manifestations and anthropometric parameters were explored in greater detail. New associations have been found and need to be reproduced in other paediatric cohorts. Given the marked variation in disease presentation, it is important to delineate the natural history of IBD in children. Predicting the disease course from the phenotype at diagnosis will help in tailoring therapy and providing appropriate counselling to both the child and family.

Chapter 6: Follow-up of South Australian children diagnosed with Inflammatory Bowel Disease

6.1: Introduction

The aim of diagnosing inflammatory bowel disease is to initiate the appropriate therapy in a timely fashion to control the disease and alter its course. Tailoring therapy according to the disease severity will optimise control, thus improving morbidity and mortality. Thus, identifying phenotypic features at diagnosis indicative of a more severe, unremitting and resistant course is important. The following chapters will describe a South Australian paediatric cohort at both diagnosis and follow-up, and potential prognostic indicators will be sought.

6.2: Aims and Hypothesis

6.2.1: Aims

- Describe the phenotypic features at diagnosis of South Australian children with IBD.
- Describe the course of IBD in South Australian children.
- Relate the disease course, including response to therapy, to phenotypic features at the time of diagnosis.

6.2.2: Hypothesis

- Disease course will be dependent upon the phenotypic features at diagnosis.
- Initial response to medical therapy within the first 16 weeks will influence subsequent disease activity.
- Early introduction of immunomodulators will have a positive impact upon disease course.

6.3: Methodology

6.3.1: Recruitment of Children

This was a retrospective case notes review of South Australian children aged less than 18 years diagnosed with IBD between the 1st of January1996 and 31st of December 2009 identified from the APAIBD database, Women's and Children's Hospital electronic records and the private notes of the only paediatric gastroenterologist (Dr Paul Hammond) who practices part-time outside of the tertiary centre.

6.3.2: Phenotypic Features at Diagnosis

Phenotypic features at diagnosis were examined by reviewing the details held in APAIBD (section 5.4.1) with the information recorded in the medical records at the Women's and Children's Hospital and Dr Paul Hammond's practice. The diagnostic subtype of CD, UC and IBDU was reviewed for each patient based on the Porto criteria and the report from the working group of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the Crohn's and Colitis Foundation of America.[16, 17] Each child's disease was assigned the Montreal classification for CD (table 3.2) and UC (table 3.3).[18] Upon reviewing the presenting symptoms, anthropometric and laboratory parameters from the case notes, a severity score was assigned. The severity score included the Paediatric Crohn's Disease Activity Index (PCDAI; table 4.2 in Appendix A) and Paediatric Ulcerative Colitis Activity Index (PUCAI; table 4.1).[126, 282, 283, 468, 469]

6.3.3: Medical therapy

The medical therapy initiated following diagnosis was recorded, and included corticosteroids, enteral nutrition, aminosalicylates, thiopurines, calcineurin inhibitors and biological agents.

6.3.4: Follow-up Data

The case notes were reviewed at specified time points following diagnosis and initiation of therapy to reassess their disease. The review times included 6 and 16 weeks (induction period) and then at one (+/- one month), two (+/- three months), five (+/- six months) and ten (+/- twelve months) years following diagnosis, and the last paediatric review during the study period or prior to transition to adult care. Information on changes in disease subtype, anatomical extent (endoscopic re-evaluation), Crohn's behaviour, extra-intestinal manifestations, laboratory parameters and anthropometric data were recorded at the review times. In addition, the clinical disease activity was assessed at these review times according to the PCDAI and PUCAI.

6.3.5: Clinical Parameters of Disease Course

Several clinical parameters of disease activity were recorded during the follow-up period. These included duration of oral/intravenous corticosteroids use, corticosteroid response, relapse of clinical disease, persistent disease, change in disease extent, progression to complicated Crohn's behaviour, hospitalisation, major surgery and anthropometric parameters. The follow-up period for analysis of the various clinical parameters was

restricted to a maximum of 5 years because the number of children with follow-up data beyond this dropped considerably.

6.3.5.1: Corticosteroid Use

The use and duration of oral (prednisolone/budesonide) and intravenous (hydrocortisone) corticosteroids was recorded. Corticosteroid response, as a measure of disease severity was described in terms of responsive, dependent or refractory:[287, 343, 470, 471]

- Responsive*:* disease entering clinical remission (PCDAI ≤ 10 or PUCAI < 10) within 4 weeks and then able to wean off corticosteroids within 16 weeks.
- Dependent*:* disease entering remission (PCDAI ≤ 10 or PUCAI < 10) but unable to cease corticosteroids within 16 weeks and/or clinical relapse within 4 weeks of cessation.
- Refractory: disease not entering clinical remission within 4 weeks.

Corticosteroid response was assessed at the end of the induction period (first 16 weeks following start of corticosteroids) and at one, two and five years. At these yearly time periods, the worst corticosteroid efficacy was recorded. Furthermore, children who required recurrent courses of corticosteroids in any year but were able to be weaned within 16 weeks with no recurrence in the next 4 weeks were still considered to be "responsive".

6.3.5.2: Clinical Disease Activity

Description of clinical disease activity over time was made in terms of relapse, remission and persistent disease.

- Relapse: clinically active disease (PCDAI of > 10 or PUCAI of ≥ 10) lasting a minimum of 7 days.
- Remission: clinically inactive disease (PCDAI ≤ 10 or PUCAI < 10) lasting at least 7 days.
- Persistent disease: clinically active disease (PCDAI of > 10 or PUCAI of ≥ 10) lasting at least 6 months with no remission.

The date and duration of a relapse and persistent disease activity was recorded.

6.3.5.3: Changes in Anatomical Disease Extent

Intestinal extent of disease in both CD and UC was reviewed whenever the child had a repeat endoscopy/colonoscopy. This usually occurred at two years following diagnosis. It was noted whether there was extension, regression or histological remission and the period of time following diagnosis. Assessment was based on the Montreal classification of disease extent for each disease subtype:[18]

CD:

- Extension: isolated terminal ileum (L1) or isolated colonic (L2) to ileocolonic disease (L3).
- Regression*:* ileocolonic (L3) to either isolated terminal ileum (L1) or isolated colonic (L2); mucosal healing/histological remission.
- Mucosal healing*:* no mucosal lesions (Grade 1) with or without histological inflammation on follow-up colonoscopy.
- Histological remission*:* no mucosal lesions and no histological inflammation.

UC:

- Extension: proctitis (E1) to either left sided (E2) or extensive colitis (E3); left sided (E2) to extensive colitis (E3).
- Regression: extensive (E3) to left sided colitis (E2) or proctitis (E3); left sided colitis (E2) to proctitis (E1); mucosal healing/histological remission.
- Mucosal healing: no mucosal lesions (Grade 1) with or without histological inflammation on follow-up colonoscopy.
- Histological remission: no mucosal lesions and no histological inflammation.

6.3.5.4: Development of Complicating Crohn's Disease Behaviour

Change in CD behaviour from inflammatory (B1) to stricturing (B2) or perforating (B3) was recorded within the period of time from diagnosis.

6.3.5.5: Hospitalisation

Total duration of hospitalisation (days) between review periods was also recorded.

6.3.5.6: Major Surgery

Major surgery was defined as resection of bowel, stoma formation, intestinal fistulectomy and removal of intra-abdominal masses/collections. Gastrostomy insertion, percutaneous drainage of intra-abdominal collections, other abdominal surgery unrelated to the intestinal

inflammation and perianal surgery were recorded as minor surgery.[76, 123, 328, 339, 472] The period of time from diagnosis to major surgery was recorded.

6.3.5.7: Anthropometric Parameters

The weight, height, height velocity and BMI parameters were recorded and z-scores calculated at each review period.[450] The height velocity was only recorded when there were sequential measures at least six months apart. The height velocity z-score was then calculated by subtracting the mean height for age and gender from the recorded height and then dividing by the standard deviation from the mean according to the table from the Fels longitudinal study.[217, 468, 473]

6.3.6: Statistical Analysis

Data from APAIBD and follow-up information were recorded into an excel spread sheet (Microsoft Excel 2007, Microsoft corporation, Redmond, WA, US). The phenotypic features at diagnosis and any potential relationship was investigated by the statistical package within Epi Info 3.5.1 (CDC, Atlanta, GA, USA), SPSS for windows 15 (SPSS Inc, Chicago, IL, USA) and SAS 9.3 (SAS Institute Inc, Cary, NC, USA). Groups of interest were compared using independent t-tests for two group comparisons and ANOVA for more than two groups when the data were normally distributed. When data was not normally distributed and not able to be transformed to normality then comparison between the two groups was undertaken by Mann-Whitney or Kruskal-Wallis testing for more than two groups. Results were presented as either means with standard errors or medians with inter-quartile range (IQR). Categorical comparison was made by chi-square analysis with results reported as corrected chi-squares (Yates). Fisher's Exact Test was used when the expected cell values were less than five in one or more cells. Confounders were investigated by means of stratification and regression modelling.

The various clinical parameters and their time to onset were assessed by the Kaplan-Meier analysis. Potential influence of phenotypic features at diagnosis on the onset of these events was sought by Cox Proportional Hazards. Corticosteroid and hospital duration within the five years following diagnosis was assessed by the negative binomial regression analysis, given the variable time period of follow-up for each child. Results were presented as mean duration of days per year, and confounders were searched and presented as a rate ratio. Analysis of anthropometric data at diagnosis and then changes during the follow-up period was

undertaken by means of linear mixed effects model (unstructured covariance). The interaction term combining IBD subtype and time period was added to the model. If this interaction term was significant, then post hoc analysis between and within the groups were made, and if the interaction term was not significant then the mixed effects model was presented. Predictors for anthropometric parameters and their subsequent changes was analysed by means of linear regression modelling. All p-values were reported as two-tailed and the significance level for rejecting the null hypotheses was taken to be 0.05.

6.3.7: Ethics Approval

Analysis of APAIBD, review of the WCH electronic database for discharge diagnosis and case notes review was approved by the hospital ethics committee.

6.4: Analysis of South Australian Cohort at Diagnosis

6.4.1: Description of Cohort at Diagnosis

There were 287 children aged less than 18 years diagnosed with IBD in South Australia between 1996 and 2009. The diagnosis was CD in 167 (58.2%), UC in 108 (37.6%) and 12 had IBDU (4.2%) as shown in table 6.4.1. There were no significant differences in the age at diagnosis between the subtypes with the median age being 12.7 years. Children with CD presented with a significantly longer duration of symptoms prior to diagnosis compared to UC (table 6.4.1).

There was a male predominance of children diagnosed with IBD (59.6%) which was significantly greater than the gender distribution of South Australian children aged less than 18 years (51.3%; p=0.006) as published in the Australian Bureau of Statistics report.[451] This significant male predominance was among those diagnosed with CD (62.9% vs 51.3% of South Australian children; p=0.0036) and not UC.[451]

Children with CD presented with poorer anthropometric data compared to UC, which was independent of duration of symptoms prior to diagnosis (table 6.4.1).

There was a significantly greater frequency of extra-intestinal manifestations (EIMs) in CD (table 6.4.1). Children with CD presented with a greater frequency of mouth ulcers (aphthous), musculoskeletal and dermatological EIMs compared to UC (table 6.4.2).

The laboratory parameters at time of diagnosis are presented in table 6.4.3. CD was associated with raised inflammatory markers (platelet count, ESR, CRP and ferritin) and lower albumin levels at diagnosis.

Table 6.4.1: Phenotypic details at diagnosis of South Australian children with IBD.

	CD (n= 167)	**UC (n= 108)**	**IBDU (n= 12)**	**IBD (n= 287)**
Median age at diagnosis (IQR)	12.8 yrs (10.8, 14.4)	12.5 yrs (9.0, 14.6)	12.8 yrs (10.3, 14.5)	12.7 yrs (10.3, 14.6)
Median duration of symptoms prior to diagnosis (diagnostic delay)	18 wks[a] (9, 40)	9 wks[a] (5, 26)	26 wks (13, 37)	12 wks (8, 32)
Male gender proportion	105 (62.9%)	61 (56.5%)	5 (41.7%)	171 (59.6%)
Family history of IBD (1st degree)	18 (10.8%)	11 (10.2%)	3 (25%)	32 (11.1%)
Extra-intestinal manifestations	96[b] (57.5%)	34[b] (31.5%)	3 (25%)	133 (46.3%)
Pre- or early puberty (Tanner stage 1/2)	50 (82%)	31 (73.8%)	4 (80%)	85 (78.7%)
Mean Wt z-score (standard error)	-0.648[c,] (0.098)	-0.015[c] (0.102)	0.221 (0.568)	-0.389 (0.074)
Mean Ht z-score (standard error)	-0.299[d] (0.091)	0.168[d] (0.093)	0.113 (0.358)	-0.116 (0.067)
Mean BMI z-score (standard error)	-0.749[e] (0.107)	-0.173[e] (0.106)	0.068 (0.629)	-0.513 (0.079)

[a]$p < 0.0001$; [b]$p=0.0004$; [c]$p < 0.0001$; [d]$p=0.001$; [e]$p <0.0001$.

Table 6.4.2: Frequency of specific extra-intestinal manifestations (EIMs) at diagnosis in South Australian children.

EIMs	**CD (n= 167)**	**UC (n= 108)**	**IBDU (n= 12)**	**IBD (n=287)**
Total number of children with EIMs	96 (57.5%)	34 (31.5%)	3 (25%)	133 (46.3%)
Musculoskeletal	39[a] (23.4%)	11[a] (10.2%)	1 (8.3%)	51 (17.8%)
Hepatobiliary	16[b] (9.6%)	14 (13%)	4[b] (33.3%)	34 (11.8%)
Dermatological	15[c] (9%)	2[c] (1.9%)	0	17 (5.9%)
Ophthalmological	4 (2.4%)	0	0	4 (1.4%)
Mouth ulcers	50[d] (29.9%)	14[d] (13%)	1 8.3%)	65 (22.6%)

[a]$p=0.009$; [b]$p=0.031$; [c]$p=0.032$; [d]$p=0.002$.

Table 6.4.3: Laboratory parameters at diagnosis among the disease subtypes (median; IQR).

Laboratory result	CD (n= 167)	UC (n= 108)	IBDU (n= 12)
Hb (g/L)	11.3 (10, 12.7)	11.6 (9.8, 13)	12.7 (11.3, 13.5)
PCV (L/L)	35.5 (32, 38)	36 (31, 39)	38 (32.5, 40)
Platelets (10^9/L)	445[a,b] (364, 630)	391[a] (294, 515)	345[b] (309, 437)
WCC (10^9/L)	9.5 (7.5, 12.6)	9.4 (7.8, 12)	9.5 (5.8, 12.8)
ESR (mm/hr)	36[c,d] (20, 60)	20[c] (7, 39)	9[d] (16, 28)
CRP (mg/L)	32[e,f] (7, 70)	7[e] (4, 17)	6[f] (5, 10)
Albumin (g/L)	33[g,h] (28, 38)	38[g] (34, 42)	41[h] (36, 44)
Ferritin (ug/L)	47[i] (17, 90)	16[i] (7, 29)	16 (6, 35)
ALT (U/L)	11 (8, 17)	14 (11, 19)	20 (12, 28)
GGT (U/L)	14 (10, 21)	11 (9, 17)	12 (11, 18)

[a]p=0.0004 ; [b]p=0.003; [c]p <0.0001; [d]p=0.001; [e]p <0.0001; [f]p=0.009; [g]p <0.0001; [h]p=0.008; [i]p <0.0001.

6.4.2: Diagnostic evaluation

Colonoscopies were undertaken in 98.6% (283/287) and upper gastrointestinal endoscopies in 86% (246/287) of the IBD cohort at diagnosis. There were ten children who had surgery for gastrointestinal symptoms and signs, and found to have CD. Of the ten who were diagnosed at the time of surgery, six had appendicectomy for presumed appendicitis and four had either a diagnostic laparoscopy or laparotomy. The median duration of hospitalisation at the time of diagnosis in the total group was 1 day (IQR: 0, 4), but half of the children (49.5%) had not required an admission and were diagnosed as a day patient at endoscopic evaluation.

6.4.3: Crohn's Disease Cohort

The anatomical distribution and disease behaviour of the 167 patients with CD is presented in table 6.4.4. The majority of children presented with ileocolonic (L3; 61.2%; 101/167) and upper gastrointestinal disease (L4; 64.8%; 107/167). Nearly half of the children presented with extensive disease (L3+L4; 44.9%; 75/167) and only three children presented with isolated upper gastrointestinal disease (L4; 1.8%; 3/167; figure 6.4.1).

The majority of the children presented with inflammatory behaviour (B1; 93.4%; 155/167) followed by stricturing (B2; 4.2%; 7/167) and penetrating behaviour (B3; 2.4%; 4/167; table 6.4.4). Isolated ileal CD (L1) was associated with complicated behaviour (B2/3; OR: 5.6; 95% CI: 1.1, 25; p=0.0218), but more specifically stricturing behaviour (B2; OR: 7.3; 95% CI: 1.5, 36.2; p=0.0143).

Orofacial disease was present in 9.7% of children (16/167) at diagnosis and perianal disease was present in nearly two third of children (61.7%; 103/167; table 6.4.4). Orofacial CD was significantly associated with perianal disease (OR: 5.0; 95% CI: 1.2, 33.2; p=0.0454). Perianal disease was present in 61.7% (103/167) of children, and the most common perianal lesions were anal tags (44.3%; 74/167) and/or fissures (45.5%; 76/167) followed by perianal fistula and/or abscesses (13.1%; 22/167).

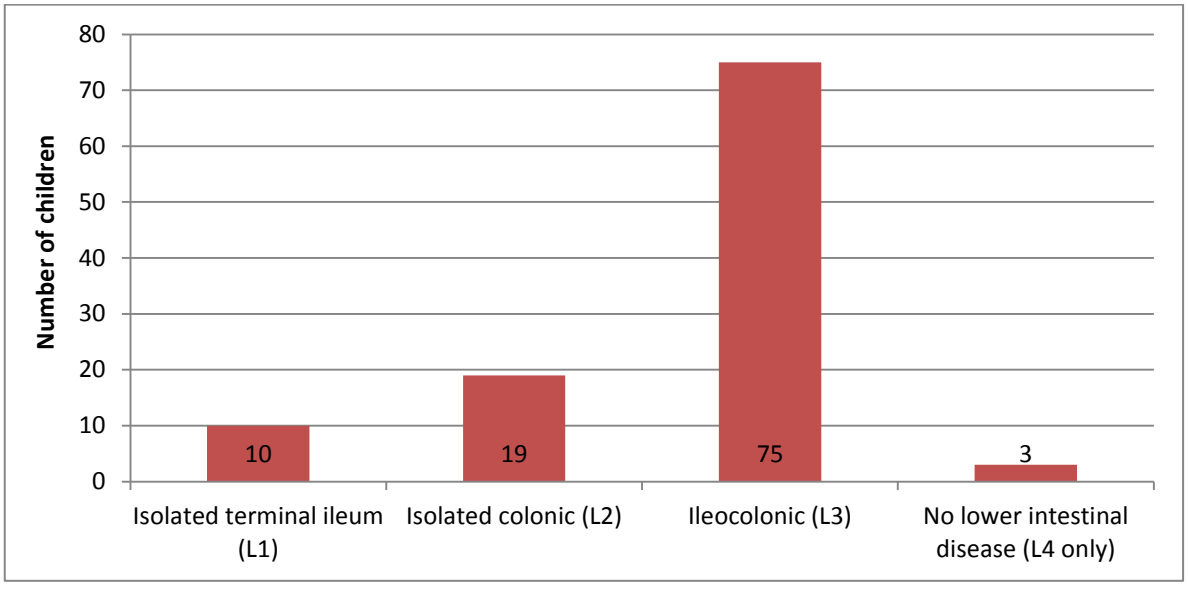
The median PCDAI score was 30 (18.7, 42.5), of which 14 children (8.8%) presented with inactive disease, 72 (45%) with mild and 74 (46.3%) with moderate-severe activity.

At least one granuloma was detected in biopsies from 35.8% of children with CD (59/165). ASCA levels were ordered in 63 children, of which 24 (38.1%) and 28 (44.4%) were positive for ASCA IgA and IgG respectively. In the patients with positive ASCA levels, the median titre for ASCA IgA was 58.6 units/ml (IQR: 44.4, 100.7) and IgG was 43.5 units/ml (IQR: 30.5, 65). Both positive ASCA IgA (OR: 15.7; 95% CI: 2, 345; p=0.0043) and IgG (OR: 20.5; 95% CI: 2.4, 453; p=0.001) titres were significantly associated with terminal ileal disease (L1/3). P-ANCA positivity was present in 18.2% (24/108) of the tested CD cohort, and it was significantly associated with L2 (isolated colonic disease) compared to L1/3 (OR: 4.6; 95% CI: 1.8, 12.3; p=0.002).

Table 6.4.4: Anatomical distribution and disease behaviour of CD in South Australian children.

	Number of children
Overall CD cohort	167
Orofacial disease	16 (9.7%)
Upper gastrointestinal disease (L4)	107 (64.8%)
Lower gastrointestinal tract	
Isolated terminal ileum (L1)	18 (10.9%)
Isolated colonic (L2)	43 (26.1%)
Ileocolonic (L3)	101 (61.2%)
Perianal	103 (61.7%)
Disease behaviour	
Inflammatory (B1)	155 (93.4%)
Stricturing (B2)	7 (4.2%)
Penetrating (B3)	4 (2.4%)

Figure 6.4.1: Extent of lower intestinal CD (L1-3) in children with upper gastrointestinal disease (L4).



6.4.4: Ulcerative Colitis Cohort

Analysis of disease distribution at the time of diagnosis in the 108 South Australian children with UC revealed the majority, 82.4% (89/108) had extensive colitis (E3), left sided colitis was present in 11.1% (12/108; E2) and proctitis (E1) in 6.5% (7/108). Among the children with extensive colitis (E3), the majority (71) had disease extending to the caecum (pancolitis). Terminal ileal involvement (backwash ileitis) was found in 11.1% (12/108), all of whom had pancolitis. Upper gastrointestinal disease was found in 27 children (13 with oesophageal, 21 with gastric and 3 with duodenal inflammation).

The median PUCAI activity score at diagnosis was 40 (IQR: 25, 55), with the severity scored as inactive in 2 (1.9%), mild in 42 (40.4%), moderate in 48 (46.2%) and severe in 12 (11.5%). Ninety-six children had p-ANCA testing, of which 56.3% were positive (54/96).

6.4.5: Discussion of South Australian Phenotype at Diagnosis

Analysis of South Australian children diagnosed with IBD revealed similarities to the rest of the Australian cohort (chapter 5). The predominance of CD, male dominance in those diagnosed with CD, distinct phenotype in both disease subtypes and associations have been thoroughly described in chapter 5.

Therefore, the South Australian cohort was representative of the wider Australian paediatric population with IBD. Given the fact that South Australia is a smaller state where health care in children aged less than 18 years of age is centralised at the one teaching centre, the Women's and Children's Hospital, and there are only four gastroenterologist managing these children, complete data collection can be achieved. Utilising such a database allows for thorough analysis of all children, accurate follow-up data and improved means of monitoring disease outcome with changes in management. This is not dissimilar to studies derived from the Olmsted County (USA)[66, 432, 441, 444] and Manitoba Province (Canada).[19, 474, 475]

There was a minority of children with CD and UC who had an inactive PCDAI $\leq$ 10 or PUCAI <10 respectively. These children were clearly symptomatic, prompting referral, further investigation and confirmation of IBD. The activity scores were more likely to be under-estimated given the fact that they were calculated retrospectively from the case notes and some important symptoms and signs may not have been documented.

6.4.6: Conclusion

The cohort of South Australian children with IBD was similar to other Australian children and international cohorts. CD was diagnosed more often than UC and there was a male dominance within this population. Other associations and differences have been described in great detail in the analysis of the national APAIBD database (chapter 5).

6.5: Induction Period (first 16 weeks following diagnosis/induction therapy)

With regard to the induction period, there were 258 children reviewed at 6 weeks and 275 at 16 weeks following diagnosis from the original cohort of 287 children. The medications initiated following diagnosis for each IBD subtype is presented in table 6.5.1.

Table 6.5.1: List of medications used for induction therapy.

	CD (n= 167)	**UC (n= 108)**	**IBDU (n= 12)**	**IBD (n= 287)**
Systemic corticosteroids	140[a] (85%)	76[a] (70%)	6 (50%)	222 (78%)
Enteral nutrition	31[b] (19%)	1[b] (1%)	0	32 (11%)
TPN	9 (5%)	3 (3%)	0	
Oral ASA	73[c] (44%)	94[c] (87%)	6 (50%)	173 (61%)
Systemic antibiotics	35 (21.3%)	5 (5%)	1 (8%)	41 (14%)
Calcineurin inhibitors	2[d] (1%)	13[d] (12%)	0	15 (5%)
Methotrexate	1 (0.6%)	0	0	1 (0.4%)
Biological agents	1 (0.6%)	0	0	1 (0.4%)
Rectal therapy (ASA/corticosteroids)	2[e] (1%)	14[e] (13%)	1 (8%)	17 (6%)

[a]p=0.006; [b]p=0.00002; [c]p<0.00001; [d]p=0.0004; [e]p=0.0002.

6.5.1: Hospitalisation

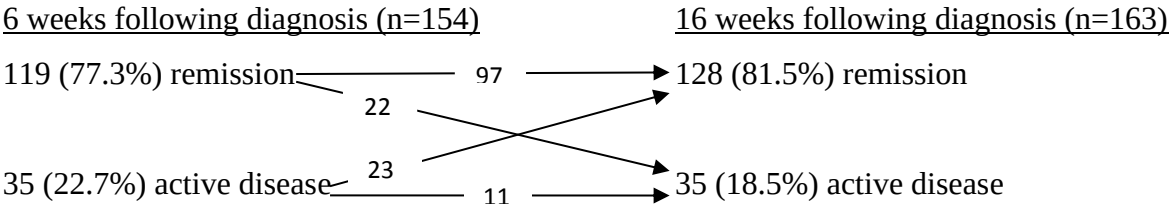
The median period of hospitalisation during induction was 1 day (IQR: 0, 5), with no significant difference between the disease subtypes.

6.5.2: Crohn's Disease

6.5.2.1: Clinical Remission Rates

Seventy-seven percent (119/154) and 78.5% (128/163) of children achieved clinical remission based on a PCDAI of ≤ 10 at 6 and 16 weeks respectively following diagnosis (figure 6.5.1). Of the 35 children who had not achieved remission at 6 weeks, two thirds (67.6%; 23) achieved remission by 16 weeks. In contrast, of the 119 children who had achieved remission at 6 weeks, 81.5% (97) were still in remission and 18.5% (22) had a relapse and continued to have active disease at 16 weeks. Overall, 11 children (6.7%) had not achieved remission at 6 and 16 weeks following diagnosis and initiation of therapy.

Figure 6.5.1: Frequency of remission (PCDAI ≤10) in children with CD.



6.5.2.2: Induction Therapy in Crohn's Disease

Nine children (5.4%; n=167) received only enteral nutrition whereas 22 children (13.2%) had enteral nutrition with systemic corticosteroids (table 6.5.1). Of the 9 children who only received enteral nutrition, 7 achieved remission at 6 and 16 weeks. Systemic corticosteroid was the predominant induction therapy in the majority of children (table 6.5.1). Corticosteroids induced clinical remission in 76% (102/134) and 77.7% (108/139) at 6 and 16 weeks respectively. There was an equal frequency of systemic corticosteroid use between those with mild compared to moderate-severe disease activity according to the PCDAI (88.9% vs 90.5%).

6.5.2.3: Predictors of Clinical Remission in Children treated with Systemic Corticosteroids

The presence of perianal disease, specifically anal tags, was associated with decreased clinical remission rates at 6 weeks (41.2% vs 71.9% with no anal tags; p=0.019) and 16 weeks (68.2 vs 86.3%; p=0.018). Children who had not attained remission at 6 weeks presented with a higher median PCDAI of 40 (IQR: 30, 45) compared to those in remission (median: 30; IQR: 20, 40; p=0.002). There was no significant difference in remission rates between those with mild (PCDAI $\leq$ 30) compared to moderate-severe activity at 6 (83.1vs 68.7%; p=0.096) and 16 weeks (73.4 vs 80.6%; p=0.44). Otherwise, there were no other predictors of clinical remission within this period.

6.5.2.4: Corticosteroid Efficacy

Corticosteroid efficacy was analysed in 135 children with CD. Of the 135 children treated with systemic corticosteroids, 91 (67.4%) were corticosteroid responsive and off corticosteroids within 16 weeks, 34 (25.2%) were corticosteroid dependent and 10 (7.4%) were corticosteroid refractory. The only phenotypic characteristic at diagnosis associated with corticosteroid responsiveness was CD behaviour. Children who presented with complicated behaviour (B2/B3) at diagnosis were more likely to be corticosteroid refractory than responsive (OR: 12.29; 95%CI: 1.57, 100.77; corrected Yates Chi-square: 7.01; p=0.013). There were no other predictors of corticosteroid response during the induction period, such as age, gender, duration of symptoms prior to diagnosis, disease extent, PCDAI severity score, presence of granuloma, EIMs and anthropometric parameters at diagnosis.

6.5.2.5: Surgery during Induction Period

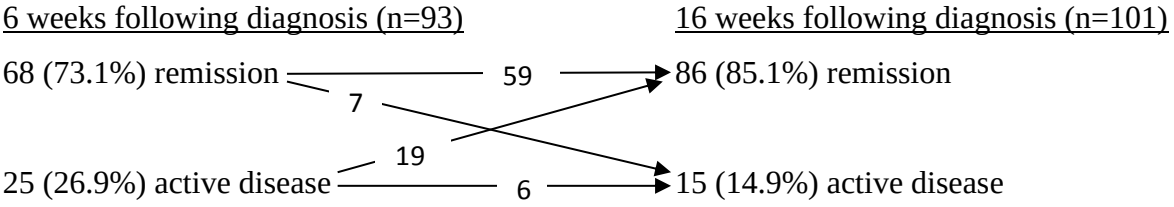
Four children out of 163 with CD (2.4%) required intra-abdominal surgery during this period. Three children had a stricture of the ileum, not resolving with medical therapy, and thus two required ileocaecal resection and one underwent a segmental resection of the ileum. The fourth child presented with a pelvic abscess and an associated enterovesical fistula requiring a sigmoid colostomy.

6.5.3: Ulcerative Colitis

6.5.3.1: Overall Clinical Remission Rates within the Induction Period

Among children diagnosed with UC, 73.1% (68/93) and 85.1% (86/101) achieved clinical remission (PUCAI < 10) at 6 and 16 weeks respectively following induction therapy. Of the 68 children who achieved remission at 6 weeks, 7 relapsed and had active disease at 16 weeks (figure 6.5.2). Within the cohort who had not attained remission at 6 weeks, 19 achieved remission by 16 weeks and 6 continued to have active disease (figure 6.5.2).

Figure 6.5.2: Frequency of remission (PUCAI <10) in children with UC.



6.5.3.2: Induction Therapy in Ulcerative Colitis

Within the induction period, oral aminosalicylates were started in 94 out of 108 children with UC (87%), irrespective of disease activity according to the PUCAI at diagnosis (table 6.5.1). Systemic corticosteroids were initiated in 76 children (70.4%; table 6.5.1). The use of systemic corticosteroids was greater in those with moderate-severe (PUCAI $\geq$ 35; 56/60; 93.3%) compared to those with mild disease (PUCAI: 10-34; 18/42; 42.9%; corrected Yates Chi-square: 29.12; $p<0.0001$) at diagnosis.

6.5.3.3: Systemic Corticosteroids as Induction Therapy

The clinical remission rates at 6 and 16 weeks following corticosteroid initiation was 74% (51/69) and 83.3% (60/72) respectively. There were no predictors at the time of diagnosis of the likelihood of achieving clinical remission during the induction period. Importantly, disease severity according to PUCAI had no impact upon remission rates.

In terms of corticosteroid efficacy, there were 43 children (60.6%) who were responsive and off corticosteroids within 16 weeks, 20 (28.2%) were dependent and 8 (11.3%) were refractory. Children who were corticosteroid refractory compared to corticosteroid responders presented with significantly lower haemoglobin, lower albumin, and higher platelet counts (table 6.5.2).

Table 6.5.2: Differences in laboratory values at diagnosis in children with UC who were corticosteroid responsive and refractory (median; IQR).

Laboratory parameters at diagnosis	Corticosteroid responsive	Corticosteroid refractory	p-value
Haemoglobin (g/L)	115 (95, 127)	88 (66, 110)	0.037
Platelets (10^9/L)	406 (294, 515)	666.5 (560, 728)	0.0047
Albumin (g/L)	38 (34, 41)	33 (27, 36)	0.0217

6.5.3.4: Calcineurin Inhibitor Use

There were 13 out of 108 children with UC (12%) who required cyclosporine during the induction period. They were treated initially with intravenous corticosteroids but due to lack of efficacy, started on cyclosporine at a median interval of 19 days (IQR: 7, 61) following corticosteroid use. Clinical and laboratory factors at diagnosis predictive of calcineurin use during the induction period are presented in table 6.5.3.

Table 6.5.3: Factors at time of diagnosis predictive of cyclosporine use in children treated with corticosteroids.

Diagnostic parameters	Cyclosporine use (median; IQR)	No Cyclosporine (median; IQR)	p-value	Cox proportional hazards	p-value
PUCAI	60 (50, 75)	45 (30, 55)	0.009	HR: 1.06 (95% CI: 1.02, 1.1)	0.004
Haemoglobin (g/L)	83 (70, 110)	116 (98, 132)	0.005	HR: 0.97 (95% CI: 0.95, 0.99)	0.002
Platelets (10^9/L)	629 (488, 699)	386 (294, 488)	0.0013	HR: 1.0 (95% CI: 1.0, 1.0)	0.0001
WCC (10^9/L)	13.25 (10.9, 16.3)	9.58 (7.9, 11.7)	0.0063	HR: 1 (95% CI: 1, 1)	0.006
Albumin (g/L)	32.5 (25, 35.5)	38 (34, 42)	0.0008	HR: 0.86 (95% CI: 0.79, 0.93)	0.0004
BMI z-score	-0.7 (-1.55, -0.21)	-0.125 (-0.85, 0.49)	0.045	HR: 0.57 (95% CI: 0.33, 0.97)	0.037

6.5.3.5: Surgery during Induction Period

Only one child required a subtotal colectomy (rectum not excised) for refractory disease during this induction period.

6.5.4: Early Use of Azathioprine during the Induction Period

The frequency of azathioprine introduction during the first 16 weeks of induction therapy was greater in children diagnosed with CD (107/167; 64%) compared to those with UC (23/108; 21%). In both disease subtypes, azathioprine was initiated during the induction period in children with a severe disease phenotype (table 6.5.4; table 6.5.5). The median period following diagnosis to initiation of azathioprine during the induction phase was 6.5 days (IQR: 0, 22.5) for CD and 13.5 days (IQR: 0, 45) for UC. Azathioprine was more frequently initiated on the day of diagnosis in both CD (35/105 children; 33.3%) and UC (7/23 children; 30.4%).

The presence of ileocolonic (L3) compared to isolated colonic (L2) involvement in CD was associated with a greater frequency of early azathioprine use (72% vs 51%; p=0.03), which was independent of other associations. Furthermore, there was a greater frequency of children with moderate-severe CD (PCDAI > 30) initiated on azathioprine (81.1 vs 55.6% with mild activity; p=0.002) during the induction phase.

With regard to UC, none of the children diagnosed with proctitis (E1)/left sided colitis (E2) were commenced on azathioprine during the induction period compared to 26% of those with extensive colitis (E3).

Table 6.5.4: Analysis of children with CD in whom azathioprine was initiated within the induction period (median; IQR).

Parameters at the time of diagnosis	Early azathioprine use (n=105)	No azathioprine (n=60)	p-value
PCDAI	35 (25, 45)	22.5 (15, 32.5)	<0.0001
Haemoglobin (g/L)	106.5 (98, 119)	124 (112, 134)	<0.0001
Platelets (10^9/L)	495 (382, 655)	411.5 (339.5, 522)	0.004
Albumin (g/L)	31 (27, 37)	36 (29.5, 42)	0.002
ESR (mm/hr)	43 (25, 68.5)	25 (11, 40)	0.0001
CRP (mg/L)	51 (16, 85)	12 (4, 33)	<0.0001

Table 6.5.5: Analysis of children with UC in whom azathioprine was initiated within the induction period (median; IQR).

Parameters at the time of diagnosis	Early azathioprine use (n=23)	No azathioprine (n=85)	p-value
PUCAI	52.5 (35, 60)	35 (25, 50)	0.01
Haemoglobin (g/L)	104 (71, 120)	120.5 (104, 131)	0.01
White cell count (10^9/L)	11.6 (8.68, 15.3)	9.02 (7.66, 10.9)	0.002
Albumin (g/L)	34.5 (28, 37)	39 (36, 42)	0.002
ESR (mm/hr)	38 (25, 60)	15.5 (6, 30)	0.002

6.5.5: Discussion of Induction Period

6.5.5.1: Clinical Remission Rates

The overall remission rates for both CD and UC at 6 and 16 weeks were in keeping with previous studies. Most of the children were treated with systemic corticosteroids in both disease subtypes (table 6.5.1).

In children diagnosed with CD and treated with corticosteroids, 77% and 81% achieved clinical remission at 6 and 16 weeks respectively. Previous studies where corticosteroids were used in paediatric CD revealed 60-80% achieved clinical remission at day 30, 71-90% at 8 weeks and 60-98% at 3 months.[285-287, 290-293, 295] There were no predictors at diagnosis associated with the decision for systemic corticosteroids, suggesting other factors may have influenced the management choice.

In the cohort with UC, the clinical remission rates following systemic corticosteroids was 74% at 6 weeks and 87% at 16 weeks, which was slightly higher than the 60-70% reported at 3 months in two previous paediatric studies.[137, 287, 309] Children with moderate-severe disease activity according to the PUCAI were more likely to be treated with systemic corticosteroids, reflecting appropriate aggressive therapy.

6.5.5.2: Predictors for Lack of Response to Systemic Corticosteroids

Children with CD presenting with stricturing and/or perforating behaviour were less likely to respond to corticosteroids, highlighting a more aggressive disease. Therefore, systemic corticosteroids may not be the appropriate therapy in those circumstances, prompting earlier

use of immunomodulators, biological agents and/or surgery. Likewise, children diagnosed with UC and presenting with evidence of more severe activity supported by worse laboratory parameters (table 6.5.2) were less likely to respond and will need rapid progression to immunomodulators or biological agents, and early consideration of surgical resection.

6.5.5.3: Comparison between Corticosteroids and Enteral Nutrition as Induction Therapy for Crohn's Disease

Both enteral nutrition and systemic corticosteroids may be used as induction therapy in those with moderate to severe disease. The use of exclusive enteral nutrition was low within this South Australian population, unlike other international centres from Europe and some North American hospital.[368, 476-478] Paediatric studies have shown similar efficacy between enteral nutrition and systemic corticosteroids in inducing clinical remission within three months.[285, 290, 295, 353, 356, 357, 479-483] However, enteral nutrition is associated with better mucosal healing and histological remission, improvement in anthropometric parameters and less adverse effects.[290, 295, 300, 480, 484-488] In this South Australian study, 7 of the 9 children who were treated exclusively with enteral nutrition achieved clinical remission within 6 weeks.

6.5.5.4: Appropriateness of Clinical Remission as a Therapeutic Goal

In this project, response to therapy could only be assessed in terms of clinical remission according to the PCDAI and PUCAI. Despite these activity indices being validated in previous studies, they were calculated based on respective data. This may have contributed to an under estimation of the score.[126, 282, 283, 469, 489]

The second issue is whether clinical remission is an appropriate therapeutic goal, or should assessment be based upon mucosal healing and/or histological remission. Attaining clinical remission may not correlate with resolution of intestinal inflammation.[295-300] In addition, mucosal lesions and microscopic inflammation may take longer to resolve. It has been shown that mucosal healing is associated with decreased risk of subsequent disease recurrence, complications, hospitalisation, systemic corticosteroids and surgical resection in CD and UC.[301-306] Undertaking endoscopic evaluation to reassess mucosal and histological changes within a few weeks of induction therapy may not be appropriate, given the need for general anaesthesia, bowel washout and the risk of colonoscopic complications. Therefore, other non-invasive markers of gut inflammation, such as faecal calprotectin, should be utilised in the assessment of disease activity.[296, 490-494]

6.5.5.5: Need for Calcineurin Inhibitors (Cyclosporine) in Ulcerative Colitis

It was not surprising that children who required cyclosporine therapy, presented with a moderate-severe disease activity, as shown by their higher PUCAI and poorer laboratory and anthropometric parameters (table 6.5.3). These results highlight the importance of clinical and laboratory monitoring of such children, with a need to consider second line therapy, such as cyclosporine or infliximab, if they do not respond to corticosteroids according to the PUCAI score on day 3 and 5.[313, 345, 495]

6.5.5.6: Early Azathioprine Use in Crohn's Disease and Ulcerative Colitis

Early initiation of azathioprine within 16 weeks following diagnosis was associated with a higher activity index and poorer laboratory parameters at diagnosis (table 6.5.4; table 6.5.5). Its lack of benefit within this time period is related to the fact that it is slow to reach maximum efficacy, taking four to six months to achieve this.

6.5.6: Conclusion

The induction period is a time to achieve early disease control with the least risk of side effects. Most of the children were treated with systemic corticosteroids and clinical remission was achieved within the first six weeks. The aim of therapy should not only be absence of symptoms but more importantly mucosal healing, as assessed by laboratory and faecal markers. Given this goal, enteral nutrition should be encouraged in Crohn's disease. The next issue is whether ongoing disease course may be predicted and altered by initial response.

6.6: Follow-up Period

The median follow-up duration of children in the IBD study group was 3.5 years (IQR: 2.2, 5.5; n=287 children). Longitudinal data was available in 249 children (86.8%) at 1 year following diagnosis, 220 children (76.7%) after 2 years, 103 children (35.9%) at 5 years and 12 children (4.2%) at 10 years. Just over half of the studied cohort with clear documentation (133/254; 52.4%) had transitioned to adult care.

6.6.1: Change in Diagnosis

There was a change in diagnosis over the follow-up period in eight children. Four children had a change within the first year, one child at 1-2 years, 2 children at 2-5 years and 1 child beyond 5 years following initial diagnosis. There were two children with an initial label of UC, who had their diagnosis revised to CD in one and the other IBDU. Of the initial cohort of 12 children with IBDU, three had their diagnosis changed to CD and two to UC. Only one child initially diagnosed with CD, was then revised to IBDU. Change in diagnosis was based on repeat radiological and endoscopic features of disease extent, subsequent finding of granulomata, growth and ongoing uncertainty of disease subtype resulting in two children reassigned as IBDU. One child had classic features of UC with pancolitis at both the initial colonoscopy and subsequent colectomy with inflammation limited to the mucosa and no granulomata. Then, he developed granulomatous inflammation of the terminal ileal stoma at seven years following initial diagnosis and now thought to have CD.

Therefore, the final distribution of disease was 170 children with CD, 108 with UC and 9 with IBDU. The median follow-up period among the disease subtypes was 3.7 years (IQR: 2.3, 5.4; n=170) for CD, 3.1 years (IQR: 2.1, 5.7; n=108) for UC and 5.3 years for IBDU (IQR: 3.3, 6.5; n=9), which was not significantly different.

6.6.2: Medications during Follow-up Period

The various medical agents used in the management of CD and UC during the follow-up period are presented in table 6.6.1. One child was treated with Trichuris suis ova and another with thalidomide, both of whom had CD.

Table 6.6.1: List of medications used in CD and UC (with the exclusion of systemic corticosteroids).

	CD (n=170)	**UC (n=108)**
Aminosalicylates	**108 (64%)**	**100 (93%)**
Initiated during induction period	73 (67.6%)	94 (94%)
Enteral nutrition	**54 (32%)**	**2 (2%)**
Initiated during induction period	31 (57%)	1
Azathioprine	**142 (84%)**	**49 (45%)**
Initiated during induction period	106 (75%)	23 (47%)
Calcineurin inhibitors	**6 (4%)**	**23 (21%)**
Initiated during induction period	2 (33%)	13 (57%)
Methotrexate	**21 (12%)**	**0**
Initiated during induction period	1 (5%)	
Biological agents	**15 (9%)**	**1 (1%)**
Initiated during induction period	1 (7%)	0

6.7: Change in Anatomical Extent of Disease

Reporting of disease extension, regression and mucosal healing was dependent upon the timing of the endoscopic re-evaluation. This usually occurred at two years following diagnosis or if disease activity continued despite medical management, and there was a need for escalating therapy or referral for surgical resection. Anatomical disease extension, regression, and mucosal healing for CD and UC are presented in figure 6.7.1, 6.7.2 and 6.7.3. Children with UC were more likely to have anatomical regression and mucosal healing within five years following diagnosis than those with CD (figure 6.7.2; 6.7.3).

Figure 6.7.1: Kaplan-Meier survival curve for anatomical disease extension in CD and UC (Wilcoxon p-value: 0.93).

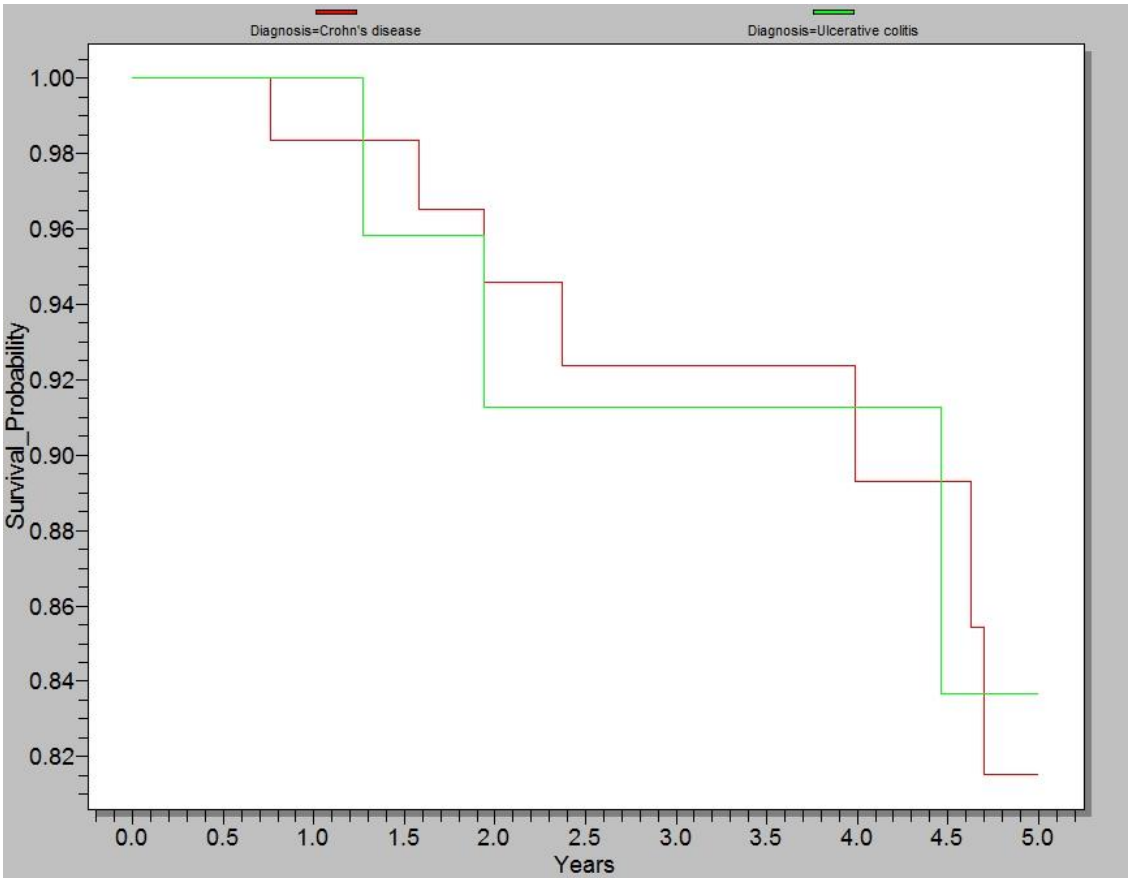


Figure 6.7.2: Kaplan-Meier survival curve for disease regression in CD and UC (Log-rank p-value: 0.0026).

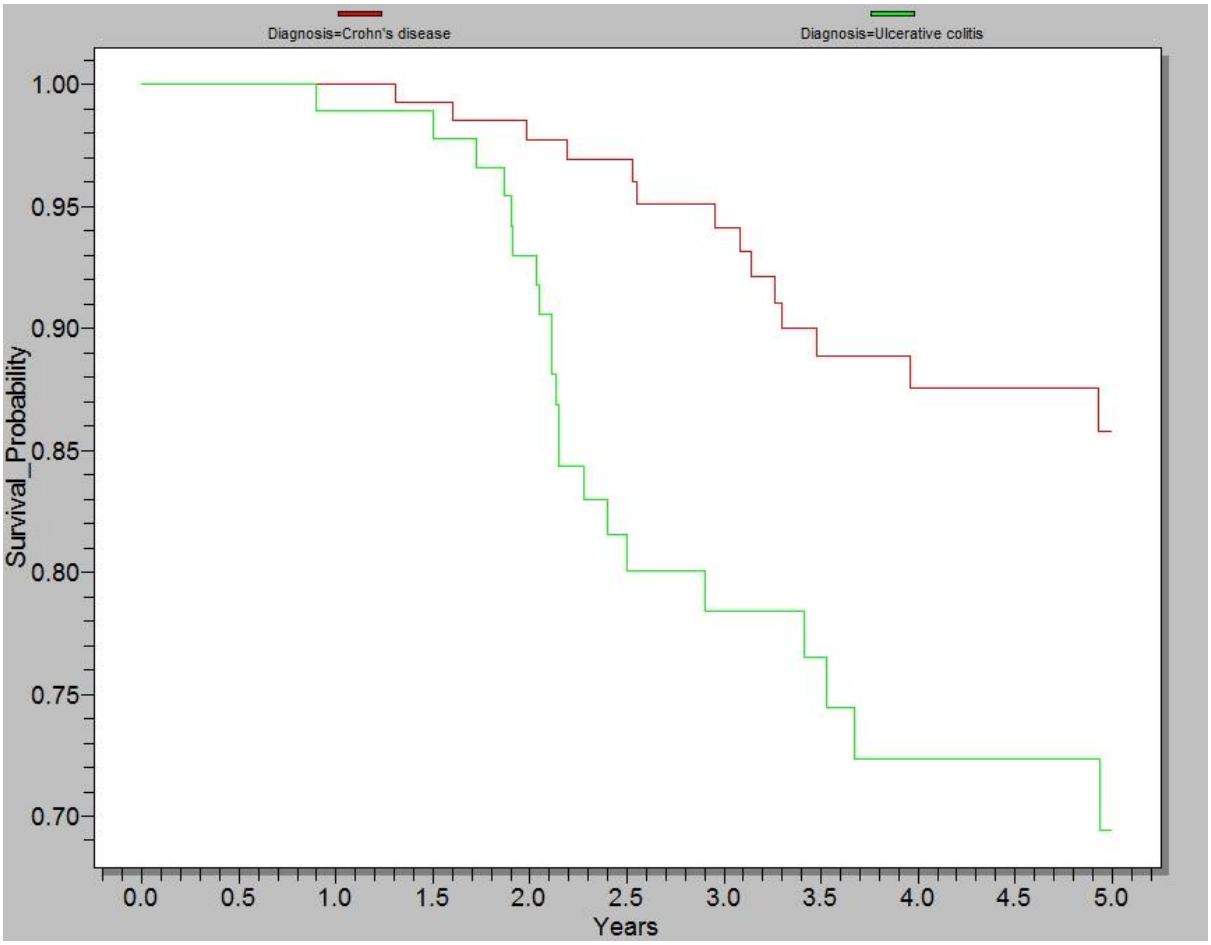
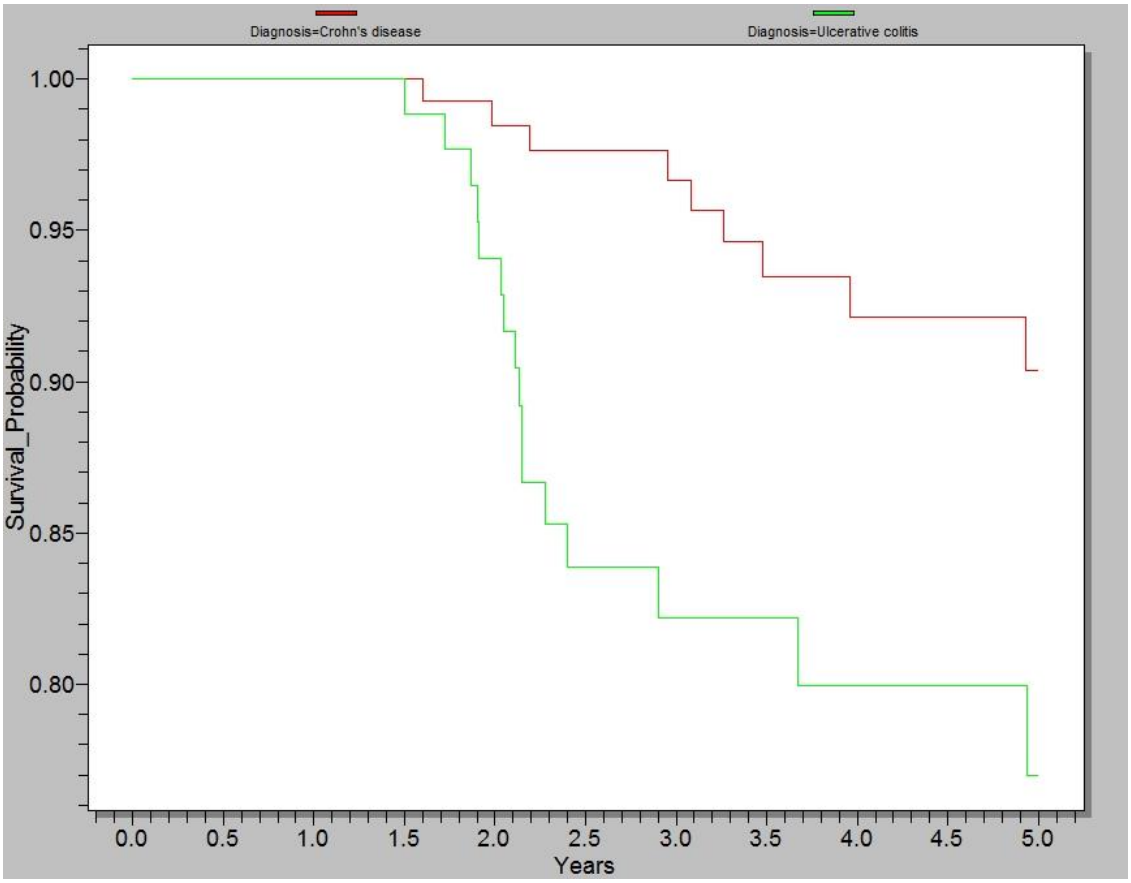


Figure 6.7.3: Kaplan-Meier survival curve for mucosal healing in CD and UC (Log-Rank p-value: 0.0037).

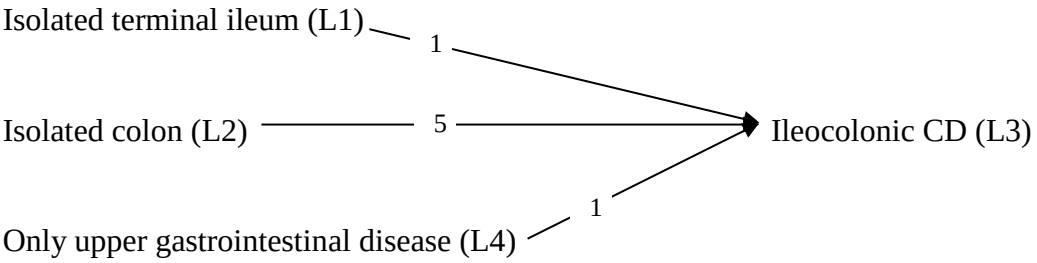


6.7.1: Crohn's Disease

6.7.1.1: Disease Extension in Crohn's Disease

Of the 64 children who presented with isolated ileal (L1) or isolated colonic disease (L2), 7 (10.9%) underwent disease extension during the follow-up period (figure 6.7.1; figure 6.7.4). There were no factors at diagnosis predictive of anatomical disease extension. Furthermore, response to initial therapy and early azathioprine use within the induction period had no impact upon anatomical extension.

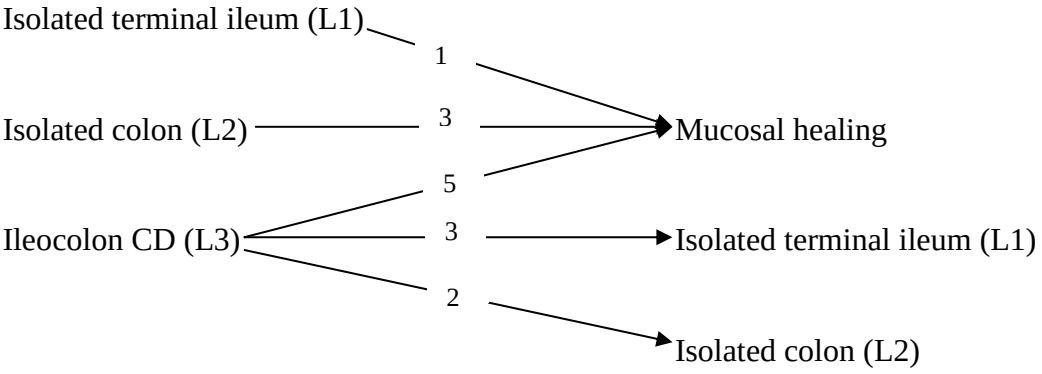
Figure 6.7.4: Extension of lower gastrointestinal involvement in children with CD within the first 5 years.



6.7.1.2: Disease Regression in Crohn's Disease

There were 14 out of the 170 children with documented lower gastrointestinal disease extent (8.2%) who underwent anatomical disease regression during the defined follow-up period of five years (figure 6.7.2). The changes in anatomical extent are shown in figure 6.7.5. The only predictor at diagnosis of disease regression was the serum albumin level (HR: 1.1; 95% CI: 1.0, 1.2; p=0.045). Disease activity (PCDAI) at diagnosis, corticosteroid efficacy, clinical remission at 6 and 16 weeks following initiation of induction therapy, and introduction of azathioprine within the first 16 weeks had no impact upon intestinal tract regression.

Figure 6.7.5: Regression in lower gastrointestinal involvement in children with CD within the first 5 years.



6.7.1.3: Mucosal Healing in Crohn's Disease

Mucosal healing occurred in 9 children (9/170; 5.3%) diagnosed with CD within 5 years following diagnosis (figure 6.7.3). All 9 children had histological remission with no inflammation. Normal serum albumin level at diagnosis was associated with mucosal healing (HR: 1.17; 95% CI: 1.02, 1.3; p=0.019). Achievement of clinical remission within the induction period, corticosteroid efficacy and/or early use of azathioprine during the induction period had no impact upon mucosal healing.

6.7.1.4: Development of Orofacial Crohn's Disease

There were 152 children (89.4%) who presented with no orofacial disease. Subsequently, two children developed orofacial disease within the first year following diagnosis.

6.7.1.5: Development of Perianal Crohn's Disease

There were 67 children (39.4%; n=170) who presented with no perianal disease. Of those with no perianal disease at diagnosis, 5 children (7.5%) developed perianal lesions within 1 year, 7 children (10.4%) between 1-2 years, and 4 children (4.5%) between 2-5 years following diagnosis.

6.7.2: Ulcerative Colitis

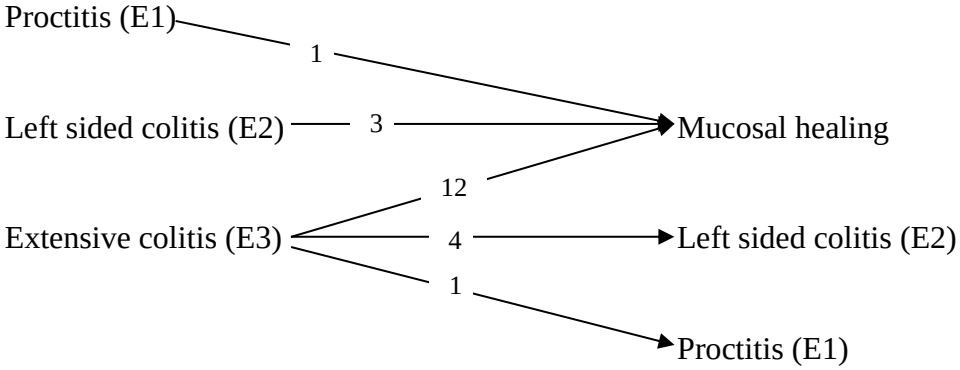
6.7.2.1: Disease Extension in Ulcerative Colitis

Three of the 19 children who presented with distal disease (E1 or E2) underwent proximal progression to extensive disease (E3) during the follow-up period. All three children initially presented with left-sided colitis (E2).

6.7.2.2: Disease Regression in Ulcerative Colitis

There were 21 children with ulcerative colitis (19.4%; n=108) who had regression of their colitis within the 5 year follow-up period (figure 6.7.2). Changes in extent of the colitis are presented in figure 6.7.6. The only factor predictive of disease regression at diagnosis was a higher haemoglobin (HR: 1.02; 95% CI: 1.0, 1.05; p=0.043). Disease activity at diagnosis (PUCAI), need for cyclosporine, response to induction therapy and introduction of azathioprine within the first 16 weeks had no impact upon regression.

Figure 6.7.6: Regression in extent of ulcerative colitis within the first 5 years.



6.7.2.3: Mucosal Healing in Ulcerative Colitis

There were 16 children (14.8%) who achieved mucosal healing of their UC within 5 years following diagnosis (figure 6.7.3). Only two children had histological remission with no evidence of inflammation. The initial endoscopic colitis score had an inverse impact upon mucosal healing (HR: 0.64; 95% CI: 0.42, 0.98; p=0.04). Otherwise, there were no other predictors of mucosal healing at diagnosis or during the induction period.

6.7.3: Progression to Intestinal Stricturing/Fistulising Complications in Crohn's Disease

There were 160 children presenting with inflammatory behaviour (B1), 6 with stricturing (B2) and 4 with penetrating (B3) disease. Of the children diagnosed with inflammatory behaviour (B1), 7 developed strictures and 4 developed penetrating complications within 5 years following diagnosis (figure 6.7.7). The Kaplan-Meier survival curve for development of stricturing/fistulising behaviour (B2/B3) is presented in figure 6.7.8.

Children diagnosed at an older age were more likely to develop intestinal strictures and/or fistulae (HR: 1.41; 95% CI: 1.02, 1.94; p=0.039). Corticosteroid refractoriness within the induction period in children with inflammatory behaviour was associated with a greater risk of complicating disease development (B2/B3; figure 6.7.9). Within the cohort of children with moderate-severe disease at diagnosis based on PCDAI, corticosteroid response within the first 16 weeks had not predicted development of complicating behaviour.

Figure 6.7.7: Changes in Crohn's disease behaviour within the first 5 years following diagnosis.

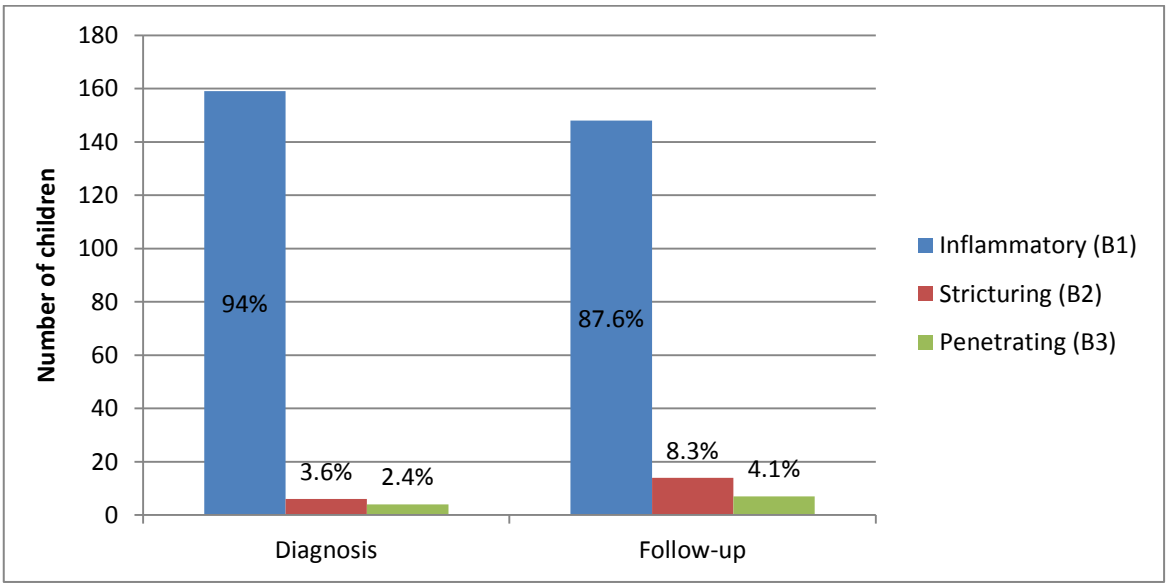


Figure 6.7.8: Kaplan-Meier survival curve for the development of intestinal stricturing/fistulising complications in CD.

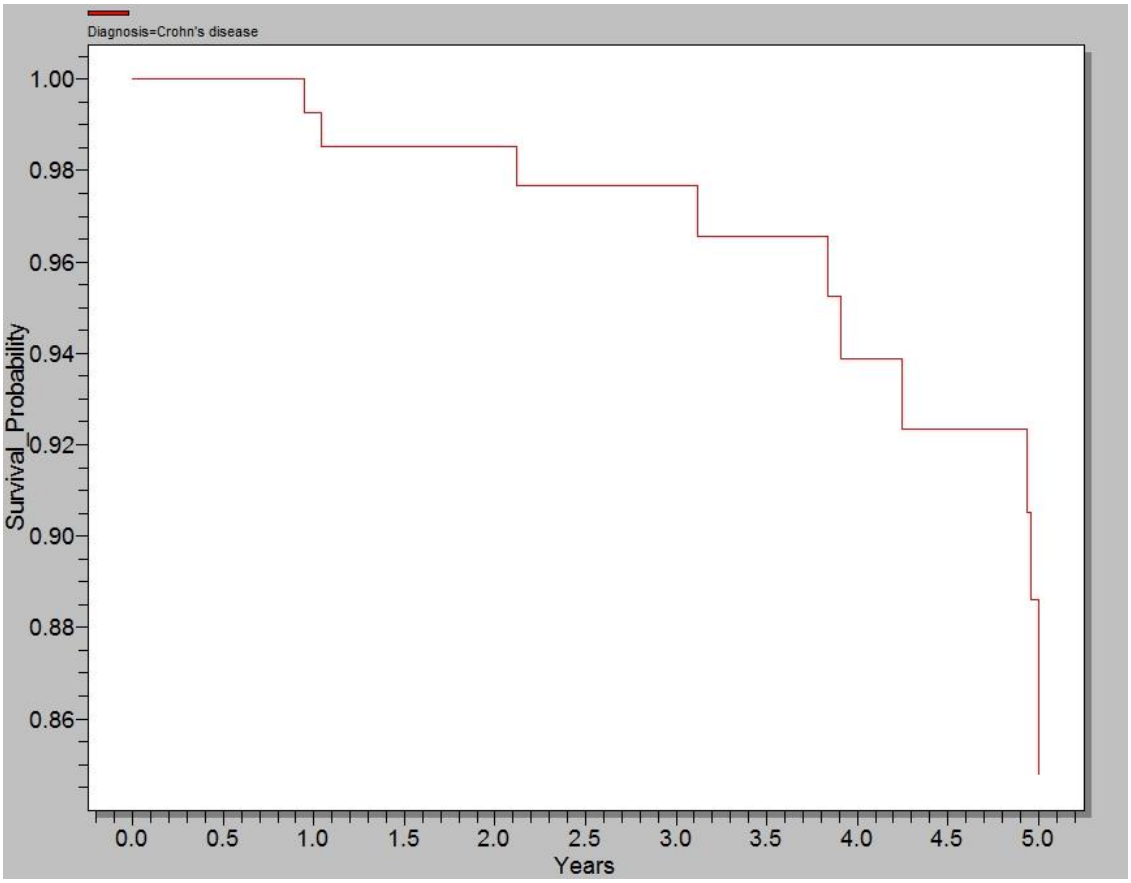
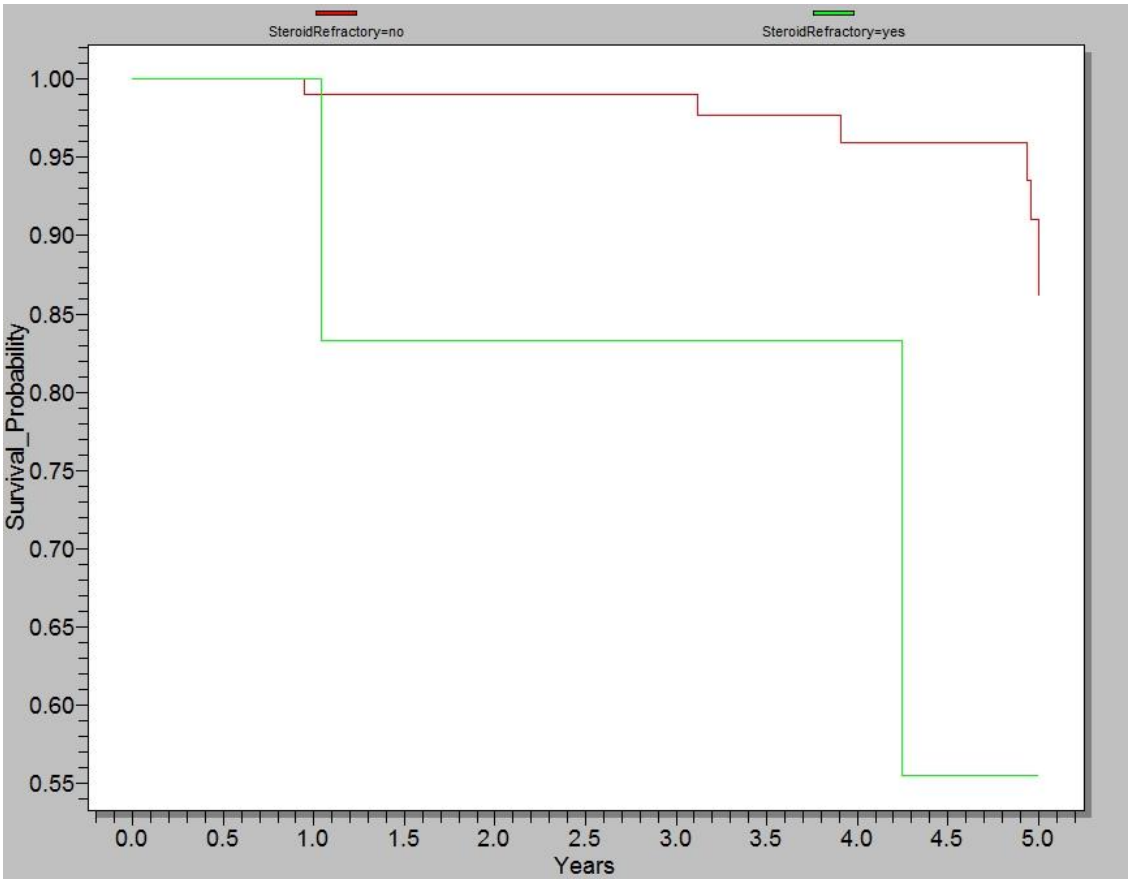


Figure 6.7.9: Development of intestinal stricturing/fistulising complications (B2/B3) in children with CD according to corticosteroid response during the induction period (Wilcoxon p-value: 0.0039).



6.7.4: Discussion of Anatomical Disease Extent Change and Complicating Behaviour Development

6.7.4.1: Anatomical Disease Extension

In both CD and UC, there was a tendency for anatomical disease extension over time, highlighting its aggressive nature. Within the first five years following diagnosis, the cumulative probability of disease extension was 18% in CD and 16% in UC (figure 6.7.1).

A Scottish paediatric study by Van Limbergen et al[75] reported that 68% of their children diagnosed with isolated terminal ileal (L1) or isolated colonic (L2) CD and followed for at least two years underwent extension to ileocolonic (L3) disease. In comparison, 31% of children reported by Vernier-Massouille et al[76] from Northern France developed involvement of an additional segment of the gastrointestinal tract (ileocolonic (L3) or upper gastrointestinal tract (L4)) when assessed at least two years after diagnosis (median follow-up period of seven years). Within the South Australian cohort, 10.4% of children underwent

anatomical extension of CD within the lower gastrointestinal tract (figure 6.7.4). There were no predictors of subsequent disease extension identified in this current study or reported previously by other authors.

In UC, 3 of the 19 South Australian children (15.8%) with distal disease (E1 or E2) underwent proximal extension of their disease (figure 6.7.1). In the Scottish paediatric study, 46% of the children with isolated proctitis (E1) or left sided colitis (E2) underwent extension of their disease when followed for at least two years.[75] Similarly, 49% of children from Northern France underwent proximal extension of their colitis over the follow-up period of at least two years (median 77 months).[134] The lower rate in this current study compared to both the Scottish and French study may have been related to the shorter maximal follow-up period of five years. In the French paediatric study, children who presented with symptoms for at least six months prior to diagnosis or have a positive first degree family history of IBD were more likely to undergo proximal extension of their colitis.[134] A search for possible predictors at diagnosis of disease extension in this South Australian study was limited by the small number of children.

6.7.4.2: Anatomical Disease Regression

This is the first paediatric study to investigate anatomical disease regression, according to the Montreal classification, following diagnosis. Any regression may alter the severity of the disease and allow for localised surgical resection if required, especially in the case of CD. Most of the children undergoing disease regression actually achieved mucosal healing/histological remission (figure 6.7.4; 6.7.6), which potentially would improve their long term outcome.

Children with UC were more likely to undergo anatomical regression of their intestinal extent (figure 6.7.2). The proportion of children achieving regression at five years following diagnosis was 14.5% in CD and 31% in UC. The only significant predictors were a serum albumin at time of diagnosis in CD and a higher haemoglobin in UC, probably reflecting a less severe phenotype.

6.7.4.3: Mucosal Healing

There was a significantly greater frequency of children achieving mucosal healing within the first five years in those diagnosed with UC compared to CD (figure 6.7.3). The frequency of mucosal healing was 8.5%, 18% and 23% for UC, and 1.5%, 3.5% and 9.5% for CD at 2, 3 and 5 years, respectively (figure 6.7.3). Most of these children had undergone histological remission. Reviewing the Kaplan-Meier survival analysis, most of the mucosal healing occurred after at least two years following diagnosis in both CD and UC, but this temporal period was dictated by the timing of the subsequent endoscopic evaluation. Mucosal healing may have occurred earlier, and the only way to have detected this would have been to submit children in clinical remission to an earlier repeat endoscopic evaluation with the associated risk of a general anaesthetic, perforation or bleeding. A more appropriate screening test for mucosal healing would have been a faecal calprotectin, which was not available in this cohort of children.

The only predictor at diagnosis for mucosal healing in CD was the serum albumin level. In the case of UC, a higher endoscopic colitis score at diagnosis, indicating increased severity, was inversely associated with mucosal healing. Previous studies have demonstrated that deep and extensive ulceration of the colon was associated with a decreased chance of achieving clinical remission and an increased risk of colectomy.[308, 315, 344, 345] The choice of induction or maintenance therapy, and initial response to therapy within the first 16 weeks was not predictive of mucosal healing in this study.

It was difficult to compare this cohort with other paediatric studies that have evaluated mucosal healing. Most paediatric studies have evaluated mucosal healing rates as an end point to assess and compare medical therapies. The majority of children in this current analysis were treated with systemic corticosteroids in the acute setting, and then azathioprine and/or aminosalicylates (UC) as maintenance therapy (table 6.5.1; table 6.6.1). Thus, there was no alternative cohort of children treated differently to allow meaningful statistical comparisons. The goal of achieving mucosal healing with medical therapy has gained importance recently, since it is associated with better long-term outcome in both CD and UC with regard to clinical disease, complications, corticosteroid use, hospitalisation and surgical resection.[301-306]

6.7.4.4: Development of Complicating Behaviour in Crohn's Disease

The cumulative probability for development of complicating disease behaviour, either stricturing (B2) or penetrating (B3) was 15% within 5 years following diagnosis (figure 6.7.8). This occurred mostly between three to five years (figure 6.7.8). It is clear that children with inflammatory behaviour at diagnosis may develop complicating behaviour over time. In the Scottish paediatric study by Van Limbergen et al,[75] the proportion of children with inflammatory behaviour (B1) decreased from 91.2% at diagnosis to 75.8% when followed for at least four years. Within the French paediatric study by Vernier-Massouille et al,[76] 71% of the children initially presented with inflammatory behaviour (B1), of whom 32% developed strictures (B2) and 11% developed penetrating intestinal complications (B3) over at least two years of follow-up (median period of follow-up was seven years). In a paediatric study by Gupta et al[169] from North America, the cumulative incidence of complicating behaviour (including perianal fistula) was 13%, 27% and 38% at 1, 5 and 10 years respectively, which was higher than this South Australian cohort. In the same study, the cumulative incidence of stricturing disease was 5.5%, 13.6% and 20.5% at 1, 5 and 10 years respectively and that of penetrating complications (including perianal fistula) was 8.2%, 17.1% and 24.5% at 1, 5 and 10 years respectively.[169]

Children diagnosed at an older age were more likely to develop complicating behaviour during the disease course. This was similarly reported in the study by Gupta et al,[71] in which children diagnosed at 6-17 years of age had a greater risk of developing strictures, abscesses and/or fistulae compared to younger children. This current study identified that corticosteroid refractoriness during the induction period was predictive of a more aggressive disease course, with development of complications (figure 6.7.9). Unlike previous studies, terminal ileal disease and ASCA positivity was not associated with the development of strictures or penetrating disease in this Australian cohort.[75, 231, 249, 318]

6.7.5: Limitations of this Study

6.7.5.1: Nature of this Study

This was a retrospective case notes review in which data collection was dependent upon the depth and accuracy of information written, with limited opportunity to question the health provider, patient or their parents. The PCDAI and PUCAI severity scores may have been under-estimated as they were calculated based on respectively gathered information using case note review.

6.7.5.2: Under-estimation of Cumulative Rates

Temporal details on anatomical disease extension, regression and mucosal healing were dependent upon the timing of subsequent endoscopic evaluation, which usually occurred at least two years following diagnosis. Thus, changes may have occurred earlier, especially in those lost to follow-up, resulting in a lower reported frequency in this study.

6.7.5.3: Differences in Statistics

In this study, the results were presented as Kaplan-Meier survival curves with the follow-up period limited to the first five years. In comparison, the Northern France and Scottish studies, conducted the same analysis in children with at least two and four years duration following diagnosis respectively, with no maximal limit on follow-up, contributing to higher published proportions.[75, 76]

6.7.6: Conclusion

The current study has highlighted that IBD is a dynamic disorder in which the extent of gastrointestinal inflammation may change and intestinal strictures and/or fistulae may develop in CD. It is important that anatomical extent and mucosal lesions are monitored, so that treatment efficacy can be assessed. There are a limited number of predictors at diagnosis of change in disease extent, but severity of the endoscopic lesions in UC is inversely related to mucosal healing. Change in anatomical extent of disease may not equate to improved disease control, unless mucosal healing or histological remission is achieved. Non-invasive markers of mucosal inflammation, such as faecal calprotectin, need to be utilised, reducing the sole reliance on clinical symptoms and frequent endoscopic evaluation as means of assessing disease control.

6.8: Description of Clinical Disease Activity

6.8.1: Subsequent Clinical Relapse following the Induction Period

6.8.1.1: Crohn's Disease

There were 130 children diagnosed with CD who achieved clinical remission at the end of the induction period. Half of the children followed for at least one year (58/116) had a subsequent relapse within the first year following diagnosis and two thirds within the first two years (table 6.8.1). The phenotypic features at diagnosis predictive of relapse are presented in table 6.8.2.

Table 6.8.1: Proportion of children with CD who achieved clinical remission during the induction period but subsequently developed a clinical relapse.

Follow-up period	**1 year**	**2 years**	**5 years**
Number of children with follow-up details.	116	103	46
Number of children who experienced at least 1 clinical relapse	58 (50%)	69 (67%)	38 (82.6%)
Median number of relapses (IQR; mode)	0.5 (0, 1; 0)	1 (0, 2; 1)	3 (2, 4; 3)
Number of children treated with induction corticosteroids.	98	87	40
Number of children treated with induction corticosteroids and subsequently experienced at least 1 clinical relapse	51 (52%)	61 (70.1%)	33 (82.5%)

Table 6.8.2: Predictive factors for at least one clinical relapse following initial remission during the induction period in children with CD (n=130).

	Relapse	**No relapse**	**p-value**	**Logistic regression modelling**
First year (n=116)				
Anal fissures at diagnosis[a] (nos of children; %)	33 (56.9%)	21 (36.2%)	0.041	OR: 2.3 (95% CI: 1.1, 4.9). p=0.027
First 2 years (n=103)				
Anal fissures at diagnosis[b,c] (nos of children; %)	38 (55.1%)	10 (29.4%)	0.025	OR: 2.9 (95% CI: 1.2, 7.1). p=0.016
Any terminal ileal disease (L1/L3) vs isolated colonic disease (L2)[d] (nos of children; %)	52 (76.5%)	18 (54.5%)	0.044	OR: 2.71 (95% CI: 1.1, 6.6). p=0.027
ASCA IgA positivity[e,f] (nos of children; %)	12 (80%)	7 (33.3%)	0.015	OR: 8.0 (95% CI: 1.7, 37.9). p=0.009
First 5 years (n=46)				
No diagnostic factors				

[a]p=0.048 (children treated with induction corticosteroids and controlling for anal tags)
[b]p= 0.016 (controlling for anal tags).
[c]p=0.003 (controlling for anal tags in children treated with induction corticosteroids).
[d]p=0.036 (controlling for disease behaviour).
[e]p=0.009 (controlling for terminal ileum disease).
[f]p=0.008 (controlling for terminal ileum disease in children treated with induction corticosteroids).

6.8.1.2: Ulcerative Colitis

There were 86 children with UC (85.1%; n=101) who achieved clinical remission at the end of the induction period. Just under half had a subsequent clinical relapse within the first year which increased to 58.9% by the end of two years (table 6.8.3). The phenotypic features at diagnosis predictive of a subsequent relapse are presented in table 6.8.4.

Table 6.8.3: Proportion of children with UC who achieved clinical remission at the end of the induction period but subsequently experienced a clinical relapse.

Follow-up period	1 year	2 years	5 years
Number of children with follow-up details who initially achieved clinical remission within the first 16 weeks.	86	73	31
Number of children who experienced at least 1 clinical relapse	37 (43%)	43 (58.9%)	24 (77.4%)
Median number of clinical relapses (IQR; mode)	0 (0, 1; 0)	1 (0, 2; 0)	2 (1, 4; 0)
Number of children treated with induction corticosteroids.	55	52	20
Number of children treated with induction corticosteroids and subsequently experienced at least 1 clinical relapse	30 (54.5%)	35 (67.3%)	16 (80%)

Table 6.8.4: Factors predictive of a clinical relapse following remission during the induction period in children diagnosed with UC (n=88).

	Relapse	**No relapse**	**p-value**	**Logistic regression modelling**
Within first year (n=80)				
Median diagnostic PUCAI[a] (IQR)	50 (35, 60)	30 (20, 50)	0.003	OR: 1.04 (95% CI: 1.01, 1.07). p=0.003
p-ANCA positivity[b] (nos of children; %)	23 (59%)	10 (33.3%)	0.06	OR: 2.9 (95% CI: 1.1, 7.7). p=0.037
Within first 2 years (n=73)				
Median diagnostic PUCAI (IQR)	45 (30, 60)	30 (20, 50)	0.007	OR: 1.04 (95% CI: 1.01, 1.07). p=0.009.
Within first 5 years (n=31)				
Median diagnostic age (IQR)	10.7 years (6.3, 13.9)	5.5 years (3.8, 8.7)	0.021	OR: 1.4 (95% CI: 1.02, 1.87). p=0.039
Median diagnostic PUCAI (IQR)	40 (30, 60)	20 (15, 40)	0.008	OR: 1.1 (95% CI: 1.02, 1.21). p=0.021.

[a]p=0.036 (children treated with induction corticosteroids).
[b]p=0.022 (correcting for extent of colitis).

6.8.2: Occurrence of Persistent Clinical Disease

The frequency of persistent clinical disease in both CD and UC are presented in figure 6.8.1 and table 6.8.5. The lack of clinical remission at the end of the induction (first 16 weeks) was associated with an increased hazard risk of subsequent persistent clinical activity in both CD (HR: 4.4; 95% CI: 1.9, 10.4; p=0.0007) and UC (HR: 7.3; 95% CI: 1.8, 29.1; p=0.005). There were no other predictors of persistent clinical disease in both disease subtypes.

Children with UC limited to the rectum (E1) developed persistent disease at a greater frequency during the five years following diagnosis on Kaplan-Meier survival analysis (figure 6.8.2; Log-Rank p-value: 0.0069). The number of children with proctitis (E1) was small as there were only six, five and two children at one, two and five years respectively following diagnosis.

Figure 6.8.1: Kaplan-Meier survival analysis of time to first persistent disease episode in children diagnosed with CD or UC (Log-Rank p-value: 0.31).

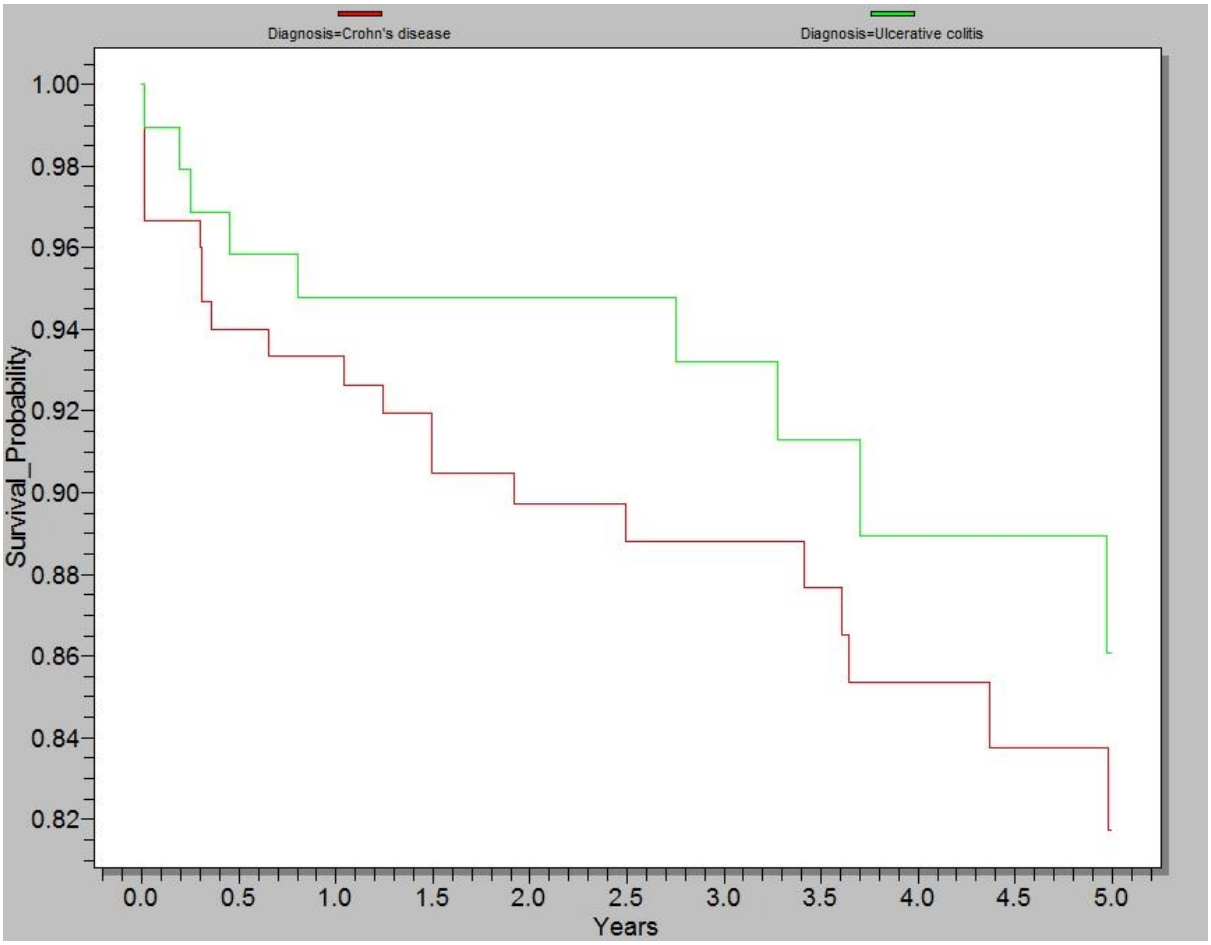
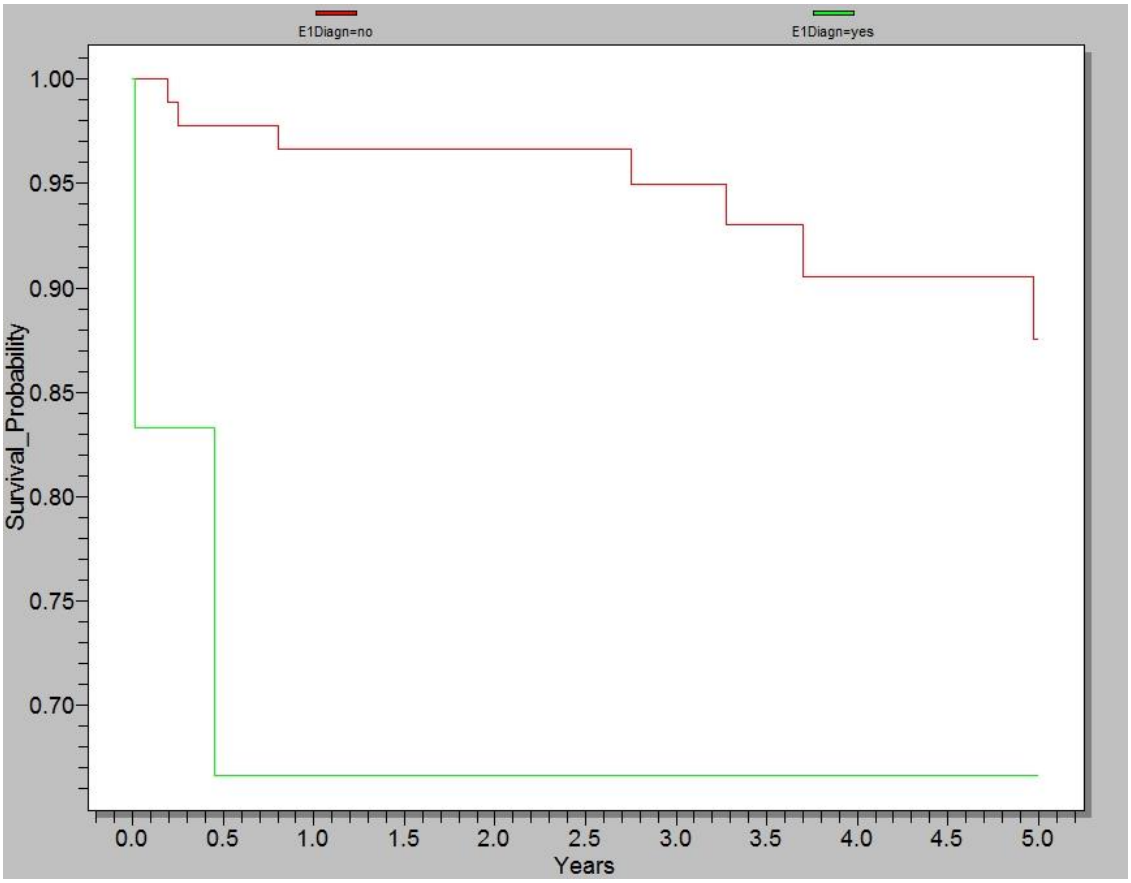


Table 6.8.5: Number of children experiencing persistent disease following diagnosis.

	1 year	2 years	5 years
Crohn's disease			
Number of children with follow-up details	148	130	64
Number of children experiencing at least 1 episode of persistent disease	8 (5.4%)	11 (8.5%)	13 (20.3%)
Number of children treated with induction corticosteroids	126	112	56
Number of children treated with induction corticosteroids and experiencing at least 1 episode of persistent disease	7 (5.6%)	11 (9.8%)	12 (21.4%)
Ulcerative colitis			
Number of children with follow-up details	95	84	38
Number of children experiencing at least 1 episode of persistent disease	4 (4.2%)	3 (3.6%)	3 (7.9%)
Number of children treated with induction corticosteroids	66	59	26
Number of children treated with induction corticosteroids and experiencing at least 1 episode of persistent disease	3 (4.5%)	3 (5.1%)	3 (11.5%)

Figure 6.8.2: Development of persistent clinical disease in children with UC limited to the rectum (E1) compared to left sided/extensive colitis (E2/3).



6.8.3: Impact of Early Introduction of Azathioprine

The early introduction of azathioprine within 16 weeks following diagnosis had no impact upon the occurrence of subsequent clinical relapse (CD: p=0.43 within first year, 0.13 within two years and 0.31 within five years; UC: p= 0.49 within first year, 0.95 within two years and 0.96 within five years) or development of persistent disease (CD: p=0.36 within first year, 0.18 within two years and 0.78 within five years; UC: p=0.69 within first year, 0.71 within two years and 0.96 within five years).

6.8.4: Discussion of Results

6.8.4.1: Risk of Subsequent Clinical Relapse

6.8.4.1.1: Crohn's Disease

Half of the children with CD developed a clinical relapse within the first year following diagnosis, which increased with ongoing follow-up (table 6.8.1). This highlights the relapsing nature of CD and choice of therapy is important in preventing clinical recurrences.

It was also interesting to note that within the first two years following diagnosis, the median and mode was one relapse, and when followed for five years then it was three relapses (table 6.8.2). In comparison, the study by Gryboski et al[182] demonstrated that the average number of clinical recurrences was one to three per year over a mean period of six and a half years. In another study in which children with CD were followed for five years, a third of the children experienced repeated exacerbations requiring systemic corticosteroids and another third experienced mild symptoms, not requiring corticosteroid therapy.[217] In this South Australian study, 82% of the children had at least one clinical relapse within the first five years which was similar to the small paediatric cohort from South-Eastern Norway in which 74% (14/19) of the children experienced a relapse during the same time period following diagnosis.[36]

The presence of anal fissures at diagnosis was associated with clinical relapse at one and two years, which has not been described before and the pathophysiological reason for this association was uncertain. There was no association with complicated perianal disease, such as fistula and/or abscesses. Disease involvement of the terminal ileum (L1/L3) and ASCA IgA positivity was associated with increased frequency of a subsequent relapse within the first two years, independent of potential confounders. This may not be surprising given the more aggressive nature of ileal CD.

6.8.4.1.2: Ulcerative Colitis

Similar to children with CD, nearly half of those with UC who achieved remission within the induction period subsequently developed a relapse within the first year (table 6.8.3). The relapse rate increased to 60% and 77% within two and five years respectively (table 6.8.3). Review of the paediatric literature reveals that approximately one third of children within any year following diagnosis will experience a relapse.[8, 137, 310, 311] In the study by Stordal et al,[36] eight of the fourteen children (57%) developed a relapse within five years. Goel et al[311] found that the disease course over a mean period of 24 years in 16 of the 25 children (64%) was characterised by clinical recurrences and remissions.

The clinical disease severity at diagnosis as described by the PUCAI score predicted a subsequent relapse in children within the first five years. No previous studies have found this association. The association between p-ANCA positivity and relapsing disease was also unique and not described previously (table 6.8.4).

6.8.4.2: Persistent Clinical Disease

The frequency of persistent clinical disease was 7.5%, 10.5% and 18.5% for CD and 5%, 5% and 13.5% for UC at one, two and five years respectively following diagnosis (figure 6.8.1). In the study by Griffiths et al,[217] 17% of the children with CD had chronic severe symptoms with no remissions despite corticosteroid therapy when followed for five years. In comparison, seven percent of children with UC had continuous symptoms in any one year following diagnosis.[137] When stratified according to disease severity at diagnosis, there were no significant difference in the frequency of continuous symptoms between those who presented with mild (4%) compared to moderate-severe activity (8%).[137]

Lack of clinical remission within 16 weeks following initiation of induction therapy predicted the occurrence of persistent clinical disease in both subtypes. This finding was not unexpected given that the induction period was defined as 16 weeks and only a further 10 weeks of clinical disease would have met the criteria for persistent disease. The lack of clinical remission within the first 16 weeks following diagnosis should have prompted a change in medical management to avoid persistent disease. Importantly, failure to achieve clinical remission at six weeks was not a significant predictor of persistent disease.

6.8.5: Limitations

6.8.5.1: Definition of Relapses and Persistent clinical Disease

The definition of a clinical remission and relapse was based on the PCDAI and PUCAI, which have been validated in previous studies.[126, 282, 283, 468, 469, 489, 496] These indices have cut-off scores for remission and severity of clinical activity, and they are assessed over seven and two days for PCDAI and PUCAI respectively.[126, 282, 468] There is no published definition for the minimum duration of lack of symptoms that would qualify as remission. In this study, the defined period was a minimum of seven days based on the details recorded in the case notes for both clinical remission and relapse. If a child had a short remission period for at least one week before recurrent clinical activity, then a new relapse was recorded. It could be argued that this was not a new episode, but instead continued disease activity.

The literature lacked a clear definition of the duration for clinical activity to define persistent disease. Review of the literature is scarce with regard to a reproducible definition. Persistent disease has been described as “persistent symptoms requiring corticosteroid treatment or equivalent without substantial remissions”.[217] Another study defined persistent disease as

"the absence of symptom-free intervals, or the presence of daily corticosteroid therapy (at least 50% of the time) to suppress symptoms, and recurrence of symptoms when the corticosteroid therapy was discontinued".[137] Persistent disease may also be described in terms of corticosteroid dependency or refractoriness, with the need for immunosuppressive medications, biological agents or surgical resection. The lack of an agreed and reproducible description of persistent disease makes comparison between studies difficult. In the current study, the presence of clinical activity according to the PCDAI and PUCAI for at least six months does have flaws given it does not incorporate therapy, and children with short duration of remission of at least one week would have not been recorded as persistent disease but instead as recurring disease course. By definition, persistent disease implies lack of response to therapeutic intervention.

6.8.5.2: Sample Size

The sample size beyond the first two years decreased by over half, which impacted upon the results (table 6.8.1; 6.8.3; 6.8.5). Children with UC who developed a subsequent clinical relapse within the first five years were significantly older (table 6.8.4), but there were actually only seven children (n=31) who had not experienced a recurrence. This significant difference may not have been present if there were a larger number of children.

6.8.5.3: Bias

Given the large decrease in the number of children beyond this time period, it may be that the children who continued to be followed were those with relapsing and/or persistent disease, whereas the other children who attained sustained remission may have been lost to follow-up. Thus, the cohort at five years may have represented a clinically more aggressive population.

6.8.6: Conclusion

This study was unique because an attempt was made to define clinical relapse and persistent disease, record all episodes and then investigate for possible predictors at diagnosis. Both CD and UC are truly a relapsing disease. Predictors at the time of diagnosis for subsequent recurrence and persistent disease were found, but need to be reproduced in a larger prospective paediatric study. It is hoped that such children can be identified at the time of diagnosis, so that appropriate induction and early effective maintenance therapy can be initiated.

6.9: Systemic Corticosteroid Use

Systemic corticosteroid use was described in terms of efficacy within the first year following diagnosis and duration (mean days per year).

6.9.1: Corticosteroid Efficacy within the First Year

6.9.1.1: Crohn's Disease

Of the 143 children who received systemic corticosteroids as induction therapy (140 initially diagnosed with CD and 3 with IBDU but then revised to CD; table 6.5.1), 136 had details recorded of the efficacy at the end of the first year. There were 83 (61%) children responsive to corticosteroids at one year following diagnosis, of which 15 required another course within the first year. Thirty-eight children (28%) were corticosteroid dependent and 15 (11%) were refractory at one year.

6.9.1.2: Ulcerative Colitis

There were 76 children treated with systemic corticosteroids as induction therapy, of which 72 children had details on corticosteroid efficacy recorded at the end of the first year (table 6.5.1). Corticosteroid efficacy at the end of the first year was responsive in 42 (58.3%), dependent in 18 (25%) and refractory in 12 (16.7%) children. Of the 42 children who were responsive to corticosteroids, 13 children (31%) required a further course of corticosteroids during the first year.

6.9.2: Predictors of Corticosteroid Refractory or Dependent Crohn's disease within the First Year

6.9.2.1: Crohn's Disease

Females with CD and children with complicated behaviour (stricturing and/or penetrating; B2/3) were more likely to be corticosteroid refractory at 1 year (table 6.9.1). Furthermore, females and those who presented with a lower BMI z-score were more likely to be corticosteroid dependent (table 6.9.1).

Table 6.9.1: Predictors of corticosteroid refractory and dependent CD at one year.

Crohn's disease	**Univariate logistic regression OR (95% CI)**	**p-value**	**Multivariate logistic regression[a,b] OR (95% CI)**	**p-value**
Corticosteroid Refractory				
Age at Diagnosis	1.39 (1.05, 1.83)	0.02	1.22 (0.85, 1.74)	0.28
Gender (female vs male)	1.74 (0.56, 5.43)	0.34	22.86 (1.99, 261.29)	**0.012**
Ileal disease (L1/3)	4.91 (1.33, 18.09)	0.017	2.92 (0.36, 23.94)	0.32
Complicating behaviour at diagnosis (B2±B3 vs B1)	6.67 (1.2, 36.91)	0.03	144.24 (1.9, 10941.15)	**0.024**
Corticosteroid Dependent				
Gender (female vs male)	2.35 (1.06, 5.21)	0.036	3.14 (1.19, 8.27)	**0.021**
BMI z-score (diagnosis)	0.73 (0.54, 0.99)	0.041	0.61 (0.41, 0.91)	**0.014**

[a]Multivariate analysis of corticosteroid refractory versus responsive included age at diagnosis, gender, pre-diagnostic duration of symptoms, initial disease extent and behaviour, diagnostic PCDAI and thiopurines use within the first 16 weeks following diagnosis.

[b]Multivariate analysis of corticosteroid dependency versus responsive included age at diagnosis, gender, pre-diagnostic duration of symptoms, initial disease extent and behaviour, diagnostic PCDAI, diagnostic BMI z-score and thiopurines use within the first 16 weeks following diagnosis.

6.9.2.2: Ulcerative Colitis

Children with UC who presented with a higher serum albumin level were less likely to be corticosteroid refractory at 1 year (OR: 0.88; 95% CI: 0.78, 0.99; p=0.044), but this significance was lost on multivariate logistic analysis when age at diagnosis, gender, pre-diagnostic duration of symptoms, disease extent, diagnostic PUCAI score and early use of azathioprine were considered (p=0.11). Higher BMI z-score at diagnosis was associated with decreased risk of being corticosteroid refractory, but this had not reached significance on both univariate (OR: 0.56; 95% CI: 0.29, 1.07; p=0.081) or multivariate analysis (OR: 0.45; 95% CI: 0.2, 1.02; p=0.056). There were no predictors for corticosteroid dependency.

6.9.3: Duration of Corticosteroid Therapy

The mean duration of corticosteroids among children with CD was 69.3 days per year (standard error: 5.42; 95% CI: 59.45, 80.79) and UC was 59.74 days per year (standard error: 5.86; CI: 49.29, 72.41) within the first five years. There was no significant difference between the disease subtypes.

6.9.3.1: Crohn's Disease

There were several features at diagnosis predictive of a longer duration of corticosteroid therapy (table 6.9.2). On multivariate analysis, increased age at diagnosis, lack of oesophageal disease, ileocolonic (L3) vs isolated colonic (L2) disease and a higher platelet count was associated with longer duration of corticosteroid within the first five years of follow-up.

Table 6.9.2: Features predictive of a longer duration of systemic corticosteroids use in children diagnosed with CD within the first five years (negative binomial regression analysis).

Features at Diagnosis	**Mean days per year (standard error; 95% CI)**	**p-value**	**Rate Ratio (95% CI) p-value**	**Multivariate Rate Ratio[a] (95% CI) p-value**
Age at diagnosis (yrs)			1.073 (1.028, 1.121) p=0.001	1.06 (1.011, 1.11) **p=0.015**
Oesophageal disease	No oesophageal: 81.3 (8.227; 66.67, 99.13) Vs Oesophageal: 47.26 (6.086; 36.71, 60.82)	0.001	1.72 (1.248, 2.372) p=0.001	1.734 (1.216, 2.474) **p=0.002**
Isolated colonic (L2) Vs Ileocolonic (L3)	L2: 43.53 (6.52; 32.46, 58.38) Vs L3: 74.57 (7.59; 61.08, 91.04)	0.002	0.584 (0.409, 0.832) p=0.003	0.657 (0.445, 0.969) **p=0.034**
Mid/late puberty (Tanner 3-5) Vs Pre/early puberty (T1-2)	Mid/late: 173.4 (55.852; 92.23, 326) Vs Pre/early: 53.78 (7.413; 41.04, 70.46)	0.034	3.224 (1.623, 6.407) p=0.001	1.815 (0.732, 4.497) p=0.198
Haemoglobin (g/L)			1.01 (1.00, 1.019) p=0.042	1.007 (0.997, 1.018) p=0.167
Platelet count (10^9/L)			0.999 (0.998, 1.000) p=0.007	0.999 (0.998, 1.000) **p=0.008**
ASCA IgG –ve Vs ASCA IgG+ve	ASCA IgG-ve: 52.44 (8.704; 37.88, 72.6) ASCA IgG+ve: 95.31 (18.373; 65.32, 139.07)	0.035	0.55 (0.334, 0.906) p=0.019	0.683 (0.388, 1.202) p=0.186

[a]Multivariate analysis with diagnostic age, gender, pre-diagnostic duration of symptoms, disease extent and behaviour, PCDAI and early use of azathioprine within the induction period.

6.9.3.2: Ulcerative Colitis

There were several features at diagnosis associated with increased mean duration of systemic corticosteroids (table 6.9.3). In contrast to CD, higher age at diagnosis was associated with a significantly decreased duration of corticosteroid use (table 6.9.3). On multivariate analysis, higher diagnostic PUCAI, extensive colitis (E3) compared to proctitis (E1), lower serum albumin and lower BMI at diagnosis contributed to longer corticosteroid use (table 6.9.3). It was interesting to note that a higher diagnostic CRP was associated with a shorter duration of systemic corticosteroid use.

Table 6.9.3: Features predictive of a longer duration of systemic corticosteroids use in children diagnosed with UC within the first five years (negative binomial regression analysis).

Features at Diagnosis	Mean days per year (standard error; 95% CI)	p-value	Rate Ratio (95% CI) p-value	Multivariate Rate Ratio[a] (95% CI) p-value
Age at diagnosis (yrs)			0.951 (0.909, 0.995) p=0.028	0.918 (0.870, 0.97) **p=0.002**
Proctitis (E1) Vs Left-sided colitis (E2)	Proctitis: 12.76 (5.26; 5.69, 28.62) Vs Left sided colitis: 55.56 (16.073; 31.52, 97.95)	0.011	0.23 (0.086, 0.616) p=0.003	0.45 (0.048, 4.188) p=0.483
Proctitis (E1) Vs Extensive colitis (E3)	Proctitis: 12.76 (5.26; 5.69, 28.62) Vs Extensive colitis: 63.58 (6.849; 51.48, 78.53)	<0.001	0.201 (0.087, 0.463) p<0.001	0.503 (0.194, 1.302) p=0.157
Endoscopic colitis score			1.275 (1.044, 1.556) p=0.017	1.132 (0.915, 1.401) p=0.252
PUCAI score			1.015 (1.003, 1.027) p=0.017	1.019 (1.004, 1.034) **p=0.012**
CRP (mg/L)			0.994 (0.989, 1.000) p=0.039	0.992 (0.986, 0.999) **p=0.025**
Albumin (g/L)			0.957 (0.922, 0.995) p=0.025	0.941 (0.896, 0.987) **p=0.013**
BMI			0.783 (0.626, 0.98) p=0.033	0.825 (0.64, 1.065) p=0.139

[a]Multivariate analysis with diagnostic age, gender, pre-diagnostic duration of symptoms, extent of colitis, endoscopic colitis score, PUCAI and early use of azathioprine within the induction period.

6.9.4: Discussion of Systemic Corticosteroid Efficacy and Duration

6.9.4.1: Corticosteroid Efficacy within the First Year

6.9.4.1.1: Crohn's Disease

At the end of the first year following diagnosis, 61% of South Australian children (83/136) were corticosteroid responsive, 28% (38/136) were dependent and 11% (15/136) were refractory. Half of the children (68/136) required only one course of corticosteroids and were in clinical remission at the end of the first year (table 6.9.4). The rates of corticosteroid efficacy were similar in the South Australian children compared to other studies utilising similar definitions (table 6.9.4). The study by Markowitz et al,[288] reported a higher corticosteroid dependency rate of 31%, but their definition was different to this study since

they included children who responded to corticosteroids and were weaned within three months but then required a second course. The study by Tung et al[287] reported lower rates of corticosteroid response/prolonged response (42%) and a higher rate of corticosteroid refractoriness (27%), which was due to the fact that their cohort extended to 1940 when immunomodulators and biological agents were not available and not initiated early in the disease course in later years.

6.9.4.1.2: Ulcerative Colitis

In this South Australian cohort of children with UC, 58.3% (42/72) were corticosteroid responsive at one year, 25% (18/72) were corticosteroid dependent and 16.7% (12/72) refractory. Just under half (40.3%; 29/72) responded to the initial course of corticosteroids and not required repeat treatment, which was similar to other studies (table 6.9.4). The study by Hyams et al[309] reported a higher rate of corticosteroid dependency (45%), but this may be due to their definition of dependency which included children who responded and were weaned off corticosteroids within 3 months but then required a subsequent course. Tung et al[287] reported a higher frequency of corticosteroid refractoriness (29%) compared to the current South Australian study, which was due to the fact that their study extended to 1940 when immunomodulators and biological agents were not available and not initiated early in the disease course during the later years (6.9.4.1.1).

Table 6.9.4: Comparison of corticosteroid efficacy at 1 year between South Australian children and other paediatric cohorts.

	Corticosteroid responsive/prolonged response (and/or subsequent course of corticosteroids)	Corticosteroid responsive/prolonged response (no further course)	Corticosteroid dependency	Corticosteroid refractory
CD				
South Australian study	61%	50%	28%	11%
Other studies	61-71%[76, 288]	46%[288]	17.2-24%[76, 322]	5%[76]
UC				
South Australian study	58.3%	40.3%	25%	16.7%
Other studies	61%[134]	50%[309]	17-26%[134, 322]	5-13%[134, 309]

6.9.4.2: Predictors of Corticosteroid Refractoriness and Dependency within the First Year

6.9.4.2.1: Crohn's Disease

The increased risk of corticosteroid refractoriness and dependency in females compared to males (table 6.9.1) has not been described previously. It was not surprising that children with more aggressive disease at time of diagnosis with stricturing or penetrating behaviour were more likely to be refractory to corticosteroid therapy. Thus, these two factors in CD would suggest close monitoring and early escalation of therapy.

Jakobsen et al[322] demonstrated that children who presented with any terminal ileal disease (isolated terminal ileum or ileocolonic) were more likely to be corticosteroid dependent, a predictive factor that was not shown in the current study. There was a positive association between proximal ileal disease and corticosteroid refractoriness, but this was not sustained when analysed for potential confounders (table 6.9.1).

The interrogation of a relationship between the diagnostic BMI z-score and corticosteroid dependency had not reached significance. There was no significant association between height z-scores at diagnosis and either corticosteroid dependency and refractoriness. In comparison, the study by Markowitz et al[288] demonstrated that falling height percentiles at the time of diagnosis was associated with increased risk of corticosteroid dependency and surgery within the first year following systemic corticosteroid treatment. Comparison was limited by

the fact that the current study had not compared the change in anthropometric parameters prior to diagnosis.

6.9.4.3: Corticosteroid Duration

6.9.4.3.1: Crohn's Disease

There were several factors impacting upon the mean duration of corticosteroids over the first five years. On multivariate analysis, increasing age at diagnosis, the lack of oesophageal inflammation and the presence of ileocolonic CD (versus isolated colonic) was associated with a significantly increased mean duration of corticosteroids per year (table 6.9.2). Interestingly, a higher diagnostic platelet count was associated with a lower mean yearly duration of systemic corticosteroids (table 6.9.2). There were no other studies reporting on corticosteroid duration in this manner. In the case of diagnostic age, for every one year rise in age, there was a 6% increase in mean corticosteroid duration. Surprisingly, there were no paediatric studies identifying predictors at diagnosis of prolonged corticosteroid duration.

6.9.4.3.2: Ulcerative Colitis

With regard to UC, a higher diagnostic PUCAI score and a lower diagnostic serum albumin was associated with increasing duration of systemic corticosteroids (table 6.9.3). For every 5 point increase in the PUCAI score, there was a 7.5% increase in corticosteroid duration and for every drop of albumin by 1g/L, there was a 5.9% increase in corticosteroid duration (table 6.9.3). Unlike CD, it was the younger children who required longer courses of corticosteroids (table 6.9.3). The interesting relationship of a lower CRP at diagnosis with prolonged corticosteroid duration could not be explained, since it would have been expected that a higher level would have this association.

6.9.4.4: Limitation of the Study

6.9.4.4.1: Description of Clinical Symptoms

In this study, response to corticosteroids was based on the validated paediatric clinical indices of PCDAI and PUCAI which was not used in other papers, except for the Markowitz et al study.[288] However, it should be noted that the PUCAI has only been proposed and published as a validated clinical scoring system since 2007.[126] Instead, other studies described clinical disease in terms of symptoms, such as frequency of bowel actions, presence of mucus or blood in the bowel actions, abdominal pain, fever and weight loss, Physician Global Assessment and/or Truelove and Witts score.[76, 134, 287, 288, 309, 322] These differences in clinical

disease description should not have had an impact upon the current reported results, given the fact that both the PCDAI and PUCAI have been validated against the Physician Global Assessment.[126, 282]

6.9.4.4.2: Definition of Corticosteroid Efficacy

There were differences in the description of corticosteroid efficacy between this study and other reported papers. In the current study, the definition was similar to that originally described by Faubion et al[321] and then adopted in the Olmsted county[287] and Northern French studies.[76, 134] On the other hand, the definition of corticosteroid dependency by the North American Pediatric Inflammatory Bowel Disease Registry was different, where children who required a subsequent course of corticosteroids within the first year despite responding in the short-term and able to be weaned off were included in the corticosteroid dependent group, whereas in our South Australian study these children were considered corticosteroid responsive.[288, 309] Another definition of corticosteroid efficacy was used by Jakobsen et al,[322] where corticosteroid dependency relied upon clinical recurrence within the first 30 days following cessation of corticosteroids, and the need for second line agents and/or corticosteroid duration of more than one year.

6.9.4.4.3: Differences in Corticosteroid Response End Points

In this study, corticosteroid responsiveness and dependency was described in terms of achieving complete clinical remission as defined by the PCDAI ≤ 10 and PUCAI < 10 for CD and UC respectively, whereas other studies have included partial remission. It might be expected that the more stringent definition of response to corticosteroid therapy may have contributed to a lower response, and higher dependency/refractory rate in the current study. Interestingly, the corticosteroid response and dependency rates were similar to other studies, but the refractory rate was higher at one year (table 6.9.4). Subsequently, the question should be asked whether the aim of therapy should be at least partial response. Complete clinical remission should be one of the goals of therapy, since this would be the best opportunity for long-term disease quiescence, if associated with mucosal healing.

6.9.4.4.4: Corticosteroid Dosing

The corticosteroid dosing in this study was not analysed. This is an important limitation given that the amount of corticosteroids per body weight over the time period may be an indirect marker of disease control, and higher dosing may increase the risk of complications. The most appropriate measure should be the accumulative corticosteroid dosing per kilogram per year. This analysis has not been reported in the medical literature with the type of corticosteroid and the dose not usually reported in other studies, impeding detailed comparison.

6.9.4.4.5: Paucity of Studies

There are a limited number of paediatric studies addressing the issue of corticosteroid response within the first year.[76, 134, 287, 288, 293, 309, 322] Most studies have reported on corticosteroid efficacy in the short term and as a comparison to other therapies, such as enteral nutrition and biological agents.

6.9.5: Conclusion

An attempt has been made to describe corticosteroid efficacy and duration over the medium to long-term. How good this is as a clinical parameter is limited by several issues. Firstly, corticosteroids are not used as maintenance therapy since they do not induce mucosal healing as well as other therapies. Secondly, they are associated with unacceptable complications in children over the medium to long-term. Thirdly, immunomodulators are usually introduced early in the disease course in children with moderate to severe activity in order to minimise exposure to corticosteroid therapy, the so called steroid sparing effect.

It is proposed that corticosteroid efficacy should be described over the short term as a means of classifying children into high and low risk of an aggressive course so that ongoing therapy may be tailored. Corticosteroid exposure as an accumulative dose per weight over a defined time period is important with regard to monitoring for the risk of long-term complications, such as growth, puberty, bone mineralisation, glucose tolerance, body habitus and associated psychological wellbeing.

6.10: Hospitalisation

6.10.1: Duration of Hospitalisation Analysis

There were no significant differences in the duration of hospitalisation between children with CD and UC. The mean duration of hospitalisation was 5.29 days/year (standard error: 0.446; 95% CI: 4.41, 6.16) in CD and 6.07 days/year (standard error: 0.645; 95% CI: 4.8, 7.33) in UC within the first five years following diagnosis between 1996 and 2009.

6.10.1.1: Predictors for Duration of Hospitalisation

6.10.1.1.1: Crohn's Disease

The predictors at the time of diagnosis of a longer duration of hospitalisation are presented in table 6.10.1. On multivariate analysis, the diagnostic features associated with longer hospitalisation included stricturing/fistulising disease behaviour, higher PCDAI score, presence of mouth ulcers, mid/late puberty, raised inflammatory markers and ASCA IgG positivity. The estimated mean duration was 6.58 (standard error: 1.643; 95% CI: 3.36, 0.9), 3.75 (standard error: 0.583; 95% CI: 2.61, 4.89) and 5.62 days per year (standard error: 0.62; 95% CI: 4.4, 6.83) for isolated terminal ileal (L1), isolated colonic (L2) and ileocolonic (L3) disease respectively. There was a significant difference in the mean duration between L2 and L3 (p=0.028). Non-response to corticosteroids during the induction period was associated with subsequent prolonged hospitalisation.

Table 6.10.1: Predictors of duration of hospitalisation in children with CD within the first five years.

	Mean days per year[a] (standard error; 95% CI)	p-value	Rate Ratio (95% CI) p-value	Multivariate Rate Ratio[b] (95% CI) p-value
Features at Diagnosis				
Age at Diagnosis (years)			1.08 (1.028, 1.134) p=0.002	1.017 (0.958, 1.081) p=0.577
Perianal fistula	Fistula: 11.86 (3.028; 5.93, 17.80) vs No fistula: 4.61 (0.409; 3.81, 5.41)	0.018	2.572 (1.514, 4.368) p <0.001	0.951 (0.255, 3.552) p=0.941
Perianal abscess	Abscess: 13.96 (3.561; 6.98, 20.94) vs No abscess: 4.43 (0.392; 3.66, 5.2)	0.008	3.149 (1.855, 5.345) p <0.001	3.356 (0.883, 12.745) p=0.075
L1/L3 vs L2	L1/L3: 5.77 (0.583; 4.63, 6.91) vs L2: 3.75 (0.583; 2.61, 4.89)	0.014	1.539 (1.07, 2.213) p=0.02	1.253 (0.82, 1.915) p=0.296
B2/B3 vs B1	B2/B3: 14.31 (4.666; 5.17, 23.46) vs B1: 4.69 (0.412; 3.88, 5.5)	0.04	3.051 (1.574, 5.914) p=0.001	2.344 (1.121, 4.901) p=0.024
PCDAI score			1.06 (1.044, 1.076) p <0.001	1.058 (1.04, 1.075) p <0.001
Mouth ulcers	Present: 3.85 (0.61; 2.65, 5.04) vs Absent: 5.89 (0.586; 4.74, 7.03)	0.016	0.654 (0.453, 0.944) p=0.023	0.403 (0.26, 0.625) p <0.001
Tanner stage 3-5 vs Tanner 1-2	Tanner 3-5: 12.05(4.106; 4.00, 20.1) vs Tanner 1-2: 3.60 (0.526; 2.57, 4.63)	0.041	3.348 (1.619, 6.923) p=0.001	3.103 (1.132, 8.508) p=0.028
Platelet count (10^9/L)			1.002 (1.001, 1.003) p=0.002	1.002 (1.001, 1.003) p=0.004
White cell count (10^9/L)			1.065 (1.034, 1.097) p <0.001	1.068 (1.032, 1.106) p <0.001
ESR (mm/hr)			1.014 (1.008, 1.021) p <0.001	1.011 (1.002, 1.019) p=0.013
CRP (mg/L)			1.012 (1.008, 1.015) p <0.001	1.01 (1.007, 1.014) p <0.001
Ferritin (µg/L)			1.005 (1.001, 1.009) p=0.008	1.002 (0.998, 1.007) p=0.27
ASCA IgG positivity	Positive: 8.17 (1.71; 4.82, 11.53) vs Negative: 3.99 (0.701; 2.61, 5.36)	0.024	2.05 (1.199, 3.502) p=0.009	4.724 (2.324, 9.603) p <0.001
Induction period				
Corticosteroid Dependent vs Responsive	Dependent: 3.76 (0.694; 2.4, 5.12) vs Responsive: 5.08 (0.589; 3.93, 6.24)	0.146	0.74 (0.482, 1.134) p=0.167	0.633 (0.394, 1.018) p=0.059
Corticosteroid Refractory vs Responsive	Refractory: 16.66 (5.383; 6.11, 27.21) vs Responsive: 5.08 (0.589; 3.93, 6.24)	0.032	3.279 (1.673, 6.425) p=0.001	2.797 (1.349, 5.8) p=0.006
Azathioprine Initiation within the Induction Period	Yes: 6.71 (0.7; 5.34, 8.08) Vs No: 2.81(0.413; 2, 3.62)	<0.001	2.386 (1.676, 3.396) p <0.001	1.384 (0.86, 2.227) p=0.181

[a]Estimated marginal means derived from the negative binomial regression analysis.

[b]Multivariate analysis with diagnostic age, gender, diagnostic delay, disease extent, disease behaviour, PCDAI, corticosteroid efficacy within the induction period and initiation of azathioprine during the induction period.

6.10.1.1.2: Ulcerative Colitis

The predictors of duration of hospitalisation within the first five years are presented in table 6.10.2. The estimated mean duration was 0, 2.39 (standard error: 0.731; 95% CI: 0.95, 3.82) and 7.12 days per year (standard error: 0.826; 95% CI: 5.5, 8.74) for isolated proctitis (E1), left sided colitis (E2) and extensive colitis (E3) respectively. There was a significant difference between E1 and E2 ($p=0.001$), E1 and E3 ($p <0.001$), and between E2 and E3 ($p <0.001$). On multivariate analysis, younger age at diagnosis, extensive colitis (E3), worsened endoscopic colitis score, lower haemoglobin, higher white cell count, raised inflammatory markers (ESR, CRP and ferritin), lower albumin, p-ANCA positivity and lower weight /BMI z-scores at diagnosis were associated with longer hospitalisation (table 6.10.2). The presence of hepatobiliary extra-intestinal manifestations at diagnosis was associated with a significantly greater mean yearly hospitalisation of 10.59 days (standard error: 2.89; 95% CI: 4.92, 16.26) compared to those without any involvement (mean: 5.33 days/year; standard error: 0.62; 95% CI: 4.12, 6.53; $p=0.021$), even when controlling for confounders ($p <0.001$), such as age at diagnosis, gender, pre-diagnostic duration of symptoms, extent of colitis, diagnostic PUCAI score, corticosteroid response and introduction of azathioprine during the induction period. Initiation of azathioprine during the induction period was associated with longer hospitalisation, despite controlling for disease severity.

Table 6.10.2: Predictors of duration of hospitalisation in children with UC within the first five years.

Parameters at Diagnosis	Mean days per year[a] (standard error; 95% CI)	p-value	Rate Ratio (95% CI) p-value	Multivariate Rate Ratio[b] (95% CI) p-value
Age at diagnosis (yrs)			1.068 (1.014, 1.125) p=0.013	0.936 (0.882, 0.994) p=0.03
Duration of symptoms prior to diagnosis (wks)			0.985 (0.976, 0.994) p=0.001	0.994 (0.982, 1.007) p=0.367
Pancolitis	Present: 7.58 (1.00; 5.61, 9.54) vs Absent: 3.37 (0.66; 2.08, 4.67)	<0.001	2.246 (1.412, 3.57) p=0.001	1.626 (0.926, 2.855) p=0.091
E3 vs E2/E1			4.373 (2.514, 7.608) p <0.001	3.918 (1.897, 8.092) p <0.001
Endoscopic colitis score[c]			1.905 (1.532, 2.369) p <0.001	1.642 (1.272, 2.12) p <0.001
PUCAI score			1.047 (1.035, 1.06) p <0.001	1.054 (1.039, 1.069) p <0.001
Haemoglobin (g/L)			0.98 (0.971, 0.99) p <0.001	0.98 (0.969, 0.992) p=0.001
Platelet count (10^9/L)			1.002 (1.001, 1.003) p=0.001	1.001 (0.999, 1.002) p=0.318
White cell count (10^9/L)			1.144 (1.085, 1.206) p <0.001	1.088 (1.032, 1.147) p=0.002
ESR (mm/hr)			1.016 (1.007, 1.026) p=0.001	1.018 (1.008, 1.029) p=0.001
CRP (mg/L)			1.016 (1.01, 1.022) p <0.001	1.013 (1.006, 1.021) p=0.001
Albumin (g/L)			0.857 (0.824, 0.891) p <0.001	0.868 (0.827, 0.911) p <0.001
Ferritin (µg/L)			1.02 (1.009, 1.032) p <0.001	1.016 (1.004, 1.028) p=0.011
p-ANCA	Positive: 8.74 (1.29; 6.22, 11.27) vs Negative: 2.11 (0.359; 1.41, 2.82)	<0.001	4.139 (2.663, 6.433) p <0.001	3.325 (1.896, 5.832) p <0.001
Weight z-score			0.683 (0.54, 0.864) p=0.001	0.625 (0.492, 0.793) p <0.001
BMI z-score			0.633 (0.513, 0.781) p <0.001	0.612 (0.486, 0.77) p <0.001
Induction period				
Corticosteroid dependent vs Responsive	Dependent: 11.38 (2.86; 5.78, 16.99) vs Responsive: 4.97 (0.813; 3.38, 6.56)	0.031	2.29 (1.273, 4.122) p=0.006	0.917 (0.437, 1.923) p=0.818
Corticosteroid refractory vs Responsive	Refractory: 10.36 (3.706; 3.09, 17.62) vs Responsive: 4.97 (0.813; 3.38, 6.56)	0.156	2.084 (0.964, 4.507) p=0.062	1.402 (0.603, 3.259) p=0.432
Azathioprine initiation	Yes: 12.41(2.792; 6.94, 17.88) vs No: 4.46 (0.54; 3.4, 5.52)	0.005	2.783 (1.687, 4.591) p <0.001	2.646 (1.401, 5.0) p=0.003

[a]Estimated marginal means derived from the negative binomial regression analysis; [b]Multivariate analysis with diagnostic age, gender, diagnostic delay, extent of colitis, PUCAI, corticosteroid response within the induction period and early azathioprine use; [c]PUCAI was excluded from the multivariate analysis for endoscopic colitis score.

6.10.2: Discussion of Hospitalisation

6.10.2.1: Duration of Hospitalisation within the First Five Years

There were no significant difference in the duration of hospitalisation between CD and UC. The estimated mean duration of hospitalisation within the first five years following diagnosis was 5-6 days per year. This was similar to that reported in the study by Heaton et al,[323] where children with CD and UC spent an average of 5.63 and 6.66 days respectively in hospital during 2006.

Within the current South Australian cohort, the potential variation in hospitalisation between 1996 and 2009 was not investigated. In contrast, a study from Ontario (Canada), demonstrated that despite the hospitalisation rate in children aged less than 18 years remaining stable between 1994 to 2004 for both CD and UC, the age adjusted odds of being hospitalised within the first three years of diagnosis was significantly greater in the 2001-2004 period for both disease subtypes.[324] Furthermore, differences in the length and rate of hospitalisation with duration following diagnosis were not investigated in the current study. The study by Gryboski[182] demonstrated that the mean duration of hospitalisation decreased following diagnosis in both CD and UC. The mean duration decreased from 12-28 days per year within the first two years following diagnosis to 2-8.4 days per year beyond four years in children with CD, and in those with UC, it decreased from 10 days per year within the first two years to 1.6 days per year beyond four years following diagnosis.[182]

6.10.2.2: Predictors of Longer Hospitalisation

6.10.2.2.1: Crohn's Disease

There were several predictors of a longer duration hospitalisation (table 6.10.1). It was not surprising that stricturing/fistulising disease behaviour at diagnosis was associated with protracted hospitalisation. In such circumstances, children would need prolonged in-hospital therapy, consisting of fasting, intravenous antibiotics, total parental nutrition and frequently surgical resection of the involved bowel.

The other associations with prolonged hospitalisation were unique findings. Possible explanations may be increased severity of disease activity at diagnosis (raised PCDAI, raised white cell count, raised platelet count, raised ESR/CRP), hormonal changes at the time of mid-late puberty and/or persistent immunological dysregulation to intra-luminal flora (ASCA

IgG positivity). Corticosteroid refractoriness within the first 16 weeks reflected a resistive type of disease that required more intensive therapy and thus prolonged hospitalisation.

The study by Gryboski[182] demonstrated that CD of the colon was associated with longer duration of hospitalisation, which was not reproduced in the current South Australian cohort. Heaton et al[323] reported that US children aged 0-5 years with CD spent a significantly longer time in hospital. In contrast, older South Australian children were at risk of longer hospitalisation on univariate analysis. For every one year increase in age there was an 8% increase in the mean hospitalisation period (table 6.10.1).

6.10.2.2.2: Ulcerative Colitis

Studies investigating potential factors predicting longer duration of hospitalisation in UC are limited. There were several features at diagnosis associated with prolonged hospitalisation in the current study (table 6.10.2). These included factors indicative of increased disease severity (raised PUCAI, lower haemoglobin, raised white cell count, raised ESR/CRP, lower albumin, raised ferritin, lower weight and lower BMI z-score). Extensive colitis and p-ANCA positivity was also associated with prolonged hospitalisation, independent of other variables (table 6.10.2).

There were conflicting associations between age at diagnosis and hospitalisation (table 6.10.2). Older children were at risk of increased hospitalisation on univariate analysis but the opposite was the case on multivariate analysis. This discrepancy may probably be due to confounding factors, such as the increased frequency of proctitis in older children. In the study by Heaton et al,[323] there was a significantly longer mean hospitalisation period (7.49 days) in children aged 11-15 years in 2006.

Children with hepatobiliary extra-intestinal manifestations had a significantly longer annual duration of hospitalisation (10.59 days/year compared to 5.33 days/year in those without any liver abnormalities) within the first five years following diagnosis. Possible reasons include the association with extensive colitis as demonstrated in the national cohort (section 5.7.1.1.1) and, the liver disease may progress despite good control of the colonic inflammation, such as the case with primary sclerosing cholangitis. [175, 176, 179, 186]

It was not surprising that corticosteroid refractoriness or dependency at the end of the induction period was associated with prolonged hospitalisation, indicating a more aggressive and resistant disease process (table 6.10.2). Introduction of azathioprine within the first 16 weeks was associated with a longer duration of hospitalisation, probably unrelated to the actual medication, but due to the fact that it was initiated in those children with a moderate to severe disease.

6.10.3: Limitation of the Study

One of the limitations of this study was that the impact and type of major surgery within the first five years was not analysed. Those children who required resection soon after diagnosis and who underwent a one-stage procedure would probably have required a shorter duration of hospitalisation. On the other hand, children who experienced protracted medically refractory disease prior to resection and/or underwent staged surgery would have spent a greater time in hospital.

The other limitation was that other disease course parameters were not assessed in terms of hospitalisation. An important course predictor would have been change in anatomical disease extent, especially mucosal healing which has been associated with reduced hospitalisation in both CD and UC.[301-306]

6.10.4: Conclusion

Several features at diagnosis and corticosteroid response within the first 16 weeks of induction therapy were identified as predictors for longer duration of hospitalisation. The presence of such predictors underlies the severe disease activity and potential for complications, prompting the clinician to aggressively step up therapy so that better control can be achieved. Not only does hospitalisation have implications for management, but it may adversely affect the child/adolescent and their family with regard to time off school and work, psychological stress and financial strain.

6.11: Major Surgery

6.11.1: Overview of Major Surgery

Forty-three children (15%; n=287) underwent major surgery during the follow-up period of five years following diagnosis, of which 31 (n=170; 18.2%) with CD, 11 (n=108; 10.2%) with UC and one (n=9; 11.1%) with IBDU. The surgical rate (with the exclusion of the one patient with UC who had a liver transplant) was higher for CD with 18.2% compared to UC with 9.3% (10/108; p=0.055). The details of the initial major surgery are presented in table 6.11.1 and 6.11.2. One child with IBDU required a subtotal colectomy with ileostomy for medically refractory disease at three years following diagnosis. The median time period from diagnosis to surgery was greater in the CD cohort (p=0.06; table 6.11.1 and 6.11.2).

Table 6.11.1: Details of initial major surgery in children with Crohn's disease.*

CD	Description
Nos of children	31 (18.2%; n=170)
Gender distribution	13 females 18 males
Median interval from diagnosis to first surgery	3.2yrs (IQR: 1.3, 5.9)
Surgical indications (nos of children)	Small bowel stricture (18) Colonic stricture (3) Intestinal perforation (10) Medically refractory (4)
Type of surgery (nos of children)	Ileocaecal resection (21) Segmental ileal stricture resection (1) Terminal ileum stricture resection (4) Ileal stricturoplasty (1) Jejunal stricture resection (1) Rectosigmoid or sigmoid colonic resection (3) Proctocolectomy (3) Appendicectomy (1) Drainage of intra-abdominal abscess (2) Ileostomy (7) Colostomy (2)
Number of children with complete disease resection	9
Number of children with post-surgical clinical remission (PCDAI ≤ 10)	22
Number of children requiring subsequent major surgery	2nd surgery (5 children) 2 further surgeries (3 children) 6 further surgeries (1 child)

*Some children underwent multiple procedures during the same surgery and underwent surgery for several indications/complications.

Table 6.11.2: Details of initial major surgery in children with ulcerative colitis.

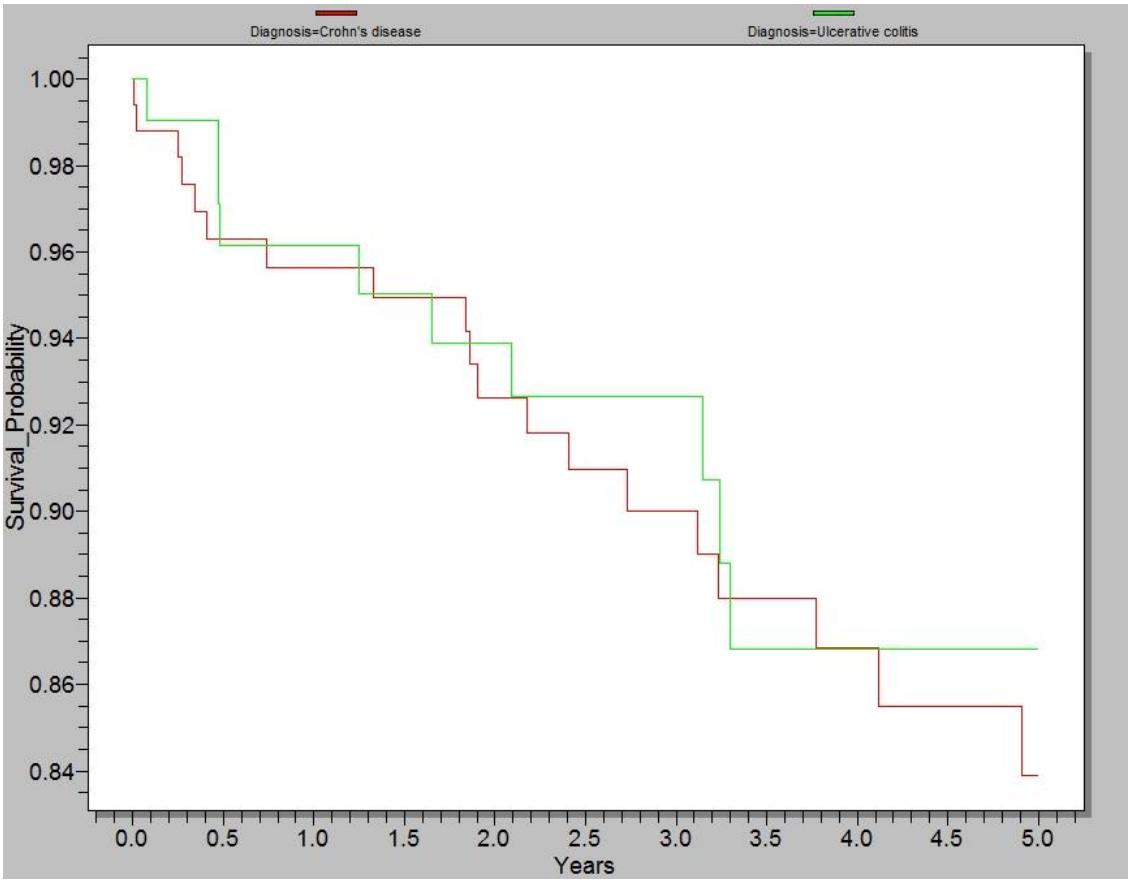
	Description
Nos of children	11 (10.2%; n=180)
Gender distribution	4 females 7 males
Median interval from diagnosis to first surgery[a]	1.4yrs (IQR: 0.5, 3.1)
Surgical indications (nos of children)	Medically refractory (10) Liver failure 2nd to PSC (1)
Type of surgery	Subtotal colectomy with ileostomy (6) Proctocolectomy (total) with ileostomy (4) Liver transplant (1)
Number of children needing subsequent surgery	8 (follow on procedures with ileoanal anastomosis and/or proctectomy)

[a]Exclusion of the patient who required a liver transplant.

6.11.2: Surgical Rates within the First Five Years

The Kaplan-Meier survival curve for the initial major surgery within the first five years following diagnosis is presented in figure 6.11.1. The surgical frequency was 4.5, 10 and 16% for CD, and 4, 7 and 13% for UC at 1, 3 and 5 years respectively (figure 6.11.1).

Figure 6.11.1: Kaplan-Meier survival curve for major surgery in children with CD and UC (Wilcoxon p-value: 0.74).*



*Exclusion of the patient with ulcerative colitis who required a liver transplant.

6.11.3: Predictors of Major Surgery within the First Five Years

The features at diagnosis that predisposed to major surgery are presented in table 6.11.3. Interestingly, complete clinical remission at 16 weeks following initiation of induction therapy, corticosteroid response within the induction period and early use of azathioprine had no impact upon the risk of having surgery in both disease subtypes.

Table 6.11.3: Predictors of major surgery within the first 5 years in children with CD or UC (Cox proportional hazards).

Predictors at Diagnosis	**Univariate analysis**
CD	
PCDAI	HR: 1.04, (95% CI: 1, 1.07) p=0.036
Stricturing (B2) vs inflammatory (B1) behaviour	HR: 21.96 (95% CI: 6.89, 69.91) p<0.001
Penetrating (B3) vs inflammatory (B1) behaviour	HR: 14.61 (95% CI: 4.09, 52.19) p<0.001
UC	
Age	HR: 1.29 (95% CI: 1, 1.66) p=0.049
PUCAI	HR: 1.08 (95% CI: 1.03, 1.12) p=0.0006
Albumin	HR: 0.9 (95% CI: 0.82, 0.99) p=0.0418
Wt z-score	HR: 0.43 (95% CI: 0.21, 0.89) p=0.02
BMI z-score	HR: 0.42 (95% CI: 0.21, 0.84) p=0.013

6.11.4: Predictors of Shorter Duration to Major Surgery

The duration to major surgery within the first five years followed a normal distribution, so potential predictors were sought by linear regression analysis. Pre-diagnostic duration of symptoms, isolated terminal ileal disease, stricturing behaviour, ASCA IgA negativity and lower height z-scores at diagnosis were predictive of a shorter duration to surgery in children with CD (table 6.11.4). In comparison, higher PUCAI score, increased severity of the colitis on initial colonoscopy and lower serum albumin at diagnosis was predictive of shorter duration to surgery in UC (table 6.11.4). Achievement of clinical remission within the induction period, initial corticosteroid response and early azathioprine use within the induction period had no impact upon the time to surgery in both CD and UC.

Table 6.11.4: Diagnostic features predictive of shorter duration to major surgery within the first five years.

Predictors at Diagnosis	**Linear regression analysis**
CD (n=19)	
Duration of symptoms prior to diagnosis (wks)	Coefficient: -0.013; standard error: 0.006; F-test: 4.5; p=0.05; Correlation coefficient (r^2): 0.21
Isolated terminal ileal disease (L1) vs ileocolonic CD (L3)	Coefficient: -2.017; standard error: 0.76; F-test: 6.97; p=0.02; Correlation coefficient (r^2): 0.33
Stricturing (B2) vs inflammatory (B1) behaviour	Coefficient: -2.154; standard error: 0.61; F-test: 12.4; p=0.004; Correlation coefficient (r^2): 0.47
ASCA IgA positivity	Coefficient: 2.805; standard error: 0.3; F-test: 87.2; p=0.0005; Correlation coefficient (r^2): 0.98
Ht z-score	Coefficient: 0.79; standard error: 0.32; F-test: 6.2; p=0.024; Correlation coefficient (r^2): 0.27
UC (n=10)	
PUCAI score	Coefficient: -0.067; standard error: 0.02; F-tes: 10.8; p=0.017; correlation coefficient (r^2): 0.61
Endoscopic colitis score	Coefficient: -1.295; standard error: 0.449; F-test: 8.3; p=0.023; correlation coefficient (r^2): 0.51
Serum albumin	Coefficient: 0.118; standard error: 0.035; F-test: 11.5; p=0.01; correlation coefficient (r^2): 0.59

6.11.5: Impact of Early Azathioprine Use

Initiation of azathioprine within the first 16 weeks following diagnosis was not protective against intra-abdominal surgery in both CD (p=0.68) and UC (p=0.26), even when controlling for disease extent and severity.

6.11.6: Discussion of Major Surgery

6.11.6.1: Surgical Rates

6.11.6.1.1: Crohn's Disease

The cumulative intra-abdominal surgical rate in South Australian children diagnosed with CD was 4.5%, 10% and 16% at 1, 3 and 5 years respectively. In comparison, other studies have reported slightly higher rates of 5-7%, 20% and 16-34% at 1, 3 and 5 years respectively during the same time period (table 6.11.5).[76, 183, 230, 324] It was interesting to note that the frequency of surgery in earlier studies were higher with rates of 30% and 50% at 3 and 5 years respectively.[266, 327, 328] The reduction in surgical rates over recent times may be due to the earlier use of immunosuppressive medications and biological agents. The study by Benchimol et al[324] from Canada, demonstrated a significant decrease in the 3 year surgical rates from 18.8% (1994-1997) to 13.6% (2001-2004; p=0.035), especially among children aged 10 years or older at diagnosis. During the same time, children were more likely to be treated with immunomodulators within the first 3 years in the period of 2001-2004 (37.8%) compared to 1994-1997 (19.6%; p=0.01).[324]

Table 6.11.5: Comparison of surgical rates in children diagnosed with CD.

Authors	Country	Year	Study population	1yr	3yr	5yr
Sedgwick et al[328]	Scotland	1968-83	Multi-centred (Scottish Hospital In-patient Statistics)			50%
Patel et al[327]	US	1968-94	Single centre		28.8%	47.2%
Freeman[266]	Canada	1979-1998	Single physician based database			39.7%
Vernier-Massouille et al[76]	France	1988-2002	EPIMAD (population based database)	7%	20%	34%
Newby et al[183]	UK	1997-2003	Multi-centred	4.9%		
Mesker et al[325]	Netherlands	1998-2007	Multi-centred			28%
Gupta et al[230]	US	2000-03	Multi-centred	5.7%		17%
Benchimol et al[324]	Canada	1994-2004	Ontario health administrative database			15.7%
Van Limbergen et al[75]	Scotland	2002-08	Multi-centred			20.2%
Current cohort	South Australia	1996-2009	APAIBD (population based database)/multi-centred	4.5%	10%	16%

6.11.6.1.2: Ulcerative Colitis

The colectomy rates in South Australian children were 4%, 7% and 13% at 1, 3 and 5 years respectively (table 6.11.6). Various studies have reported colectomy rates of 3-8%, 13-15% and 20-26% at 1, 3 and 5 years during the same study period (table 6.11.6).[75, 134, 183, 324, 497] Colectomy rates in our South Australian children beyond the first year after diagnosis were lower. In comparison, the highest rate was that reported from Utah, but this was a single centre study, where children with severe and medically resistant disease were treated and those with mild disease were more likely managed in the community and not registered in the database.[340]

Conflicting information on changes in resection rates over time have been published. Michener et al[341] reported a decrease in rates from 48.9% (1955-1964) to 26.3% (1965-1974), while Lindberg et al[14] reported a change from 12.5% (1984-1989) to 1.2% (1990-1995) in a small cohort. In contrast, two recent studies from Canada have shown that resection rates have remained stable during 1994-2004 in Ontario[324] and 1983-2009 in Calgary.[342]

Table 6.11.6: Comparison of colectomy rates in children with UC.

Authors	Country	Year	Study population	1yr	3yr	5yr
Michener et al[341]	UK	1955-1974	Single centre			
Sedgwick et al[339]	UK	1983-1987	Multi-centred (Scottish Hospital In-patient Statistics)			15%
Hyams et al[137]	USA	1967-1994	Two centres	5%		19%
Lindberg et al[14]	Sweden	1984-1995	Multi-centred			
Gower-Rousseau et al[134]	France	1988-2002	EPIMAD (population based database)	8%	15%	20%
Kelley-Quon et al[497]	USA	1999-2003	Multi-centred (PedIBDC)	4%		
Newby et al[183]	UK	1997-2003	Multi-centred	2.9%		
Howarth et al[212]	UK	2000-2003	Single centre			
Benchimol et al[324]	Canada	1994-2004	Ontario health administrative database		12.7%	
Moore et al[340]	USA	1997-2007	Single centre	16.7%	35.6%	
Van Limbergen et al[75]	Scotland	2002-2008	Multi-centred			26.1%
Current cohort	South Australia	1996-2009	APAIBD (population based database)/multi-centred	4%	7%	13%

6.11.6.2: Predictors of Surgery

6.11.6.2.1: Crohn's Disease

Within the South Australian cohort, an increased PCDAI at diagnosis, reflecting a more severe disease activity, was predictive of major surgery within the first five years. This study has not demonstrated any relationship between inflammation of the jejunum and/or ileum, deep and extensive ulceration on colonoscopy, raised white cell count, hypoalbuminaemia and ASCA positivity with subsequent surgery as reported in previous studies.[182, 230, 231, 249, 266, 308, 319, 332] It was not surprising that stricturing (B2) or perforating (B3) behaviour was associated with an increased hazard risk for intra-abdominal surgery, given that the definitive management in these circumstances would be resection of the involved bowel. Similarly, the study by Gupta et al[230] demonstrated that the risk of surgery was greater in those who subsequently developed strictures, abscesses and/or fistula.

6.11.6.2.2: Ulcerative Colitis

There were several predictors of resection identified within this study (table 6.11.3). Children who presented with a higher PUCAI score at diagnosis were at increased risk of surgery.[137, 212] In the study by Hyams et al,[137] the risk of colectomy was significantly greater in those presenting with moderate-severe compared to mild disease at 1 (8 vs 1%) and 5 years (26 vs 9%; $p<0.03$). The association between older age at diagnosis, lower serum albumin and

poorer nutritional state at diagnosis with increased resection rates has been described previously.[8, 340, 497] In the study by Kelley-Quon et al,[497] based on a large North American paediatric cohort, diagnostic albumin of less than 35g/L ($p<0.001$), weight loss ($p=0.001$) and a first degree family history of UC ($p<0.001$) was associated with an increased overall colectomy rate, and weight loss influenced earlier resection rates within the first two years ($p<0.001$). The presence of deep and extensive mucosal ulceration on colonoscopy predicted increased colectomy rates, especially during an admission of severe colitis.[315, 344, 345] In the study by Moore et al,[340] raised white cell count and decreased haematocrit was associated with an increased risk of colectomy. Therefore, the current South Australian study has reinforced that increased disease activity at diagnosis as demonstrated by an increased PUCAI, decreased albumin and decreased weight/BMI z-score, and older age at diagnosis is associated with an increased risk of colectomy (table 6.11.3). It is important that these children are treated aggressively in the hope of avoiding surgical resection.

6.11.6.3: Shorter Interval to Surgery

6.11.6.3.1: Crohn's Disease

Within the cohort of children with CD who underwent intra-abdominal surgery, there were several factors predicting shorter duration to surgery within the first five years following diagnosis (table 6.11.4). These included longer duration of symptoms prior to diagnosis, decreased height z-scores and ASCA IgA negativity. The presence of colonic involvement in those with terminal ileal disease (L3 vs L1) increased the duration to surgery, which may underline a protective effect (table 6.11.4). In an adult study by Sands et al,[472] the presence of small bowel disease without colonic involvement was associated with earlier surgery within the first three years. It was not surprising that the presence of stricturing disease (B2) at diagnosis shortened the progression to surgery, since medical therapy was more likely to fail in established fibrotic strictures.

6.11.6.3.2: Ulcerative Colitis

In children requiring a colectomy within the first five years, a higher PUCAI score, increased endoscopic colitis score and decreased serum albumin at diagnosis predicted a shorter interval (table 6.11.4). All these factors reflected a more severe disease presentation. The colitis score was in keeping with previous studies, in which the presence of deep and extensive ulceration during an admission with severe colitis was associated with increased risk of colectomy during the same admission.[315, 344]

6.11.6.4: Impact of Early Azathioprine Use

Within this South Australian cohort, the early introduction of azathioprine within the first 16 weeks following diagnosis had no protective impact against intra-abdominal surgery in both CD and UC. This may be related to the small number of children, retrospective nature of this study, other concurrent medication and/or lack of standardisation of medical management among the various doctors. The literature provides conflicting information on whether azathioprine reduces the risk of surgery in both disease subtypes.[76, 149, 498-505]

6.11.7: Limitation

6.11.7.1: Small Cohort

One of the limitations within the current study was the low number of children. There were 31 children with CD, 10 with UC and 1 with IBDU who underwent major surgery. In addition, there was a dramatic decrease in the number of children followed beyond five years, which meant that the analysis was limited to this period of time. Twelve children with CD were excluded from further analysis because they had surgery beyond the five year follow-up period. Therefore, the size of this cohort may have hindered the identification of a possible association. In addition, further analysis with regard to disease recurrence post-operatively, subsequent surgery, and changes in surgical rates over time could not be undertaken.

6.11.7.2: Retrospective Review of Case-notes/Electronic Database

Capture of children with IBD undergoing surgery, with regard to date of surgery, type of procedure and histology, was thought to be complete in those less than 18 years of age as it would have only occurred in the one institution (Women's and Children's Hospital) in South Australia. Data in those aged above 18 years may not have been complete. Surgery in other state government hospitals were sought by reviewing the state-wide electronic database, but those managed by private gastroenterologist and operated upon in non-government hospitals may have been missed. Contacting these older patients and seeking permission to gain details from their managing physician was not done in the current study.

6.11.8: Conclusion

Within the South Australian cohort, the rates of intra-abdominal surgery within the first five years were better than other studies. Several factors at diagnosis contributing towards surgery were found. It is important to identify such children so that aggressive medical management may be initiated early. The balance between retaining the lower gastrointestinal tract and the impact of ongoing inflammation upon the many facets of a child/adolescent's health is important and the decision for surgical resection may be difficult. It is hoped that with improvements in medical management, surgical resection rates could be reduced.

6.12: Growth

6.12.1: Analysis of Growth

The number of children with anthropometric parameters recorded at the defined review periods following diagnosis are presented in table 6.12.1. Details on Tanner stage (puberty) were poor as there were only 106 (38.1%) children who had this recorded out of the 278 children diagnosed with CD or UC. There were 53 children with CD (82.8%; total=64) and 31 with UC (73.8%; total=42) who were pre/early pubertal (Tanner stage 1 or 2) at diagnosis and subsequently followed (table 6.12.2).

Table 6.12.1: Number of children with recorded anthropometric values at the various follow-up time points.

Time points	**Diagnosis**	**1yr**	**2yrs**	**5yrs**
Overall number of children				
CD	170	148	131	64
UC	108	94	83	37
Weight data				
CD	166 (97.6%)	133 (89.9%)	123 (93.9%)	55 (85.9%)
UC	102 (94.4%)	84 (89.4%)	73 (88%)	29 (78.4%)
Height data				
CD	163 (95.9%)	129 (87.2%)	116 (88.5%)	52 (81.3%)
UC	99 (91.7%)	76 (80.9%)	63 (75.9%)	26 (70.3%)
BMI data				
CD	163 (95.9%)	129 (87.2%)	116 (88.5%)	52 (81.3%)
UC	99 (91.7%)	76 (80.9%)	63 (75.9%)	26 (70.3%)

Table 6.12.2: Number of children in Tanner stage 1 or 2 (pre/early puberty) at diagnosis and reviewed at the specified time periods.

Time points	**Diagnosis**	**1yr**	**2yrs**	**5yrs**
Overall number of children				
CD	53	50	44	27
UC	31	28	26	19
Weight data				
CD	52	46	42	27
UC	31	24	23	16
Height data				
CD	51	45	41	27
UC	30	21	18	15
BMI data				
CD	50	45	41	27
UC	30	21	18	15

The mean values for weight, height and BMI z-scores in children at diagnosis and then at the specific follow-up time points are presented in table 6.12.3 and 6.12.4. There were no gender related differences in the mean weight, height and BMI z-scores at diagnosis in children with CD or UC.

Table 6.12.3: Mean values (standard error) for weight, height and BMI z-scores in children with CD.

Crohn's disease	**Diagnosis**	**1yr**	**2yrs**	**5yrs**
All children				
Weight z-scores	-0.6374[a,b,c] (0.0909)	-0.0112[a,d] (0.0864)	-0.0214[b,t] (0.0884)	-0.2883[c,d,t] (0.1128)
Height z-scores	-0.2848 (0.0832)	-0.3588 (0.0828)	-0.2681 (0.0830)	-0.4004 (0.1083)
BMI z-scores	-0.7259[e,f,g] (0.0973)	0.204[e,h] (0.0831)	0.1168[f,i,n] (0.0869)	-0.0955[g,h,i,n] (0.1002)
Pre/early puberty (Tanner stage 1/2)				
Weight z-scores	-0.8906[j,k,l] (0.1738)	-0.2242[j,m] (0.1630)	-0.1430[k,u] (0.1676)	-0.4514[l,m,u] (0.1726)
Height z-scores	-0.4932 (0.1537)	-0.6098 (0.1513)	-0.4847 (0.1493)	-0.6057 (0.1627)
BMI z-scores	-0.8491[o,p,q] (0.1851)	0.193[o,r] (0.1426)	0.1880[p,s] (0.1579)	-0.0988[q,r,s] (0.1517)

[a,b,e,f,g,j,o,p,q]p<0.0001; [c]p=0.0002; [d]p=0.0023; [e]p=0.0023; [h]p=0.0007; [i]p=0.0102; [l]p=0.0014; [m]p=0.0494; [n]p=0.0026; [r]p=0.0128; [s]p=0.0074; [t]p=0.0015; [u]p=0.0026.

Table 6.12.4: Mean values (standard error) for weight, height and BMI z-scores in children with UC.

Ulcerative colitis	**Diagnosis**	**1yr**	**2yrs**	**5yrs**
All children				
Weight z-scores	-0.0344[a] (0.1151)	0.1622[a] (0.1093)	0.1269 (0.1125)	0.0647 (0.1501)
Height z-scores	0.1417 (0.1059)	0.0903 (0.1056)	0.0506 (0.1066)	0.0336 (0.1473)
BMI z-scores	-0.1746[b,c] (0.1241)	0.126[b] (0.1069)	0.1031[c] (0.1133)	-0.0056 (0.1377)
Pre/early puberty (Tanner stage 1 or 2)				
Weight z-scores	-0.1019 (0.2264)	0.1243 (0.2157)	0.1055 (0.2224)	0.0658 (0.2269)
Height z-scores	0.1437 (0.2015)	0.1478 (0.2007)	0.1992 (0.2003)	0.1650 (0.2190)
BMI z-scores	-0.2670 (0.2416)	0.0903 (0.1958)	0.0761 (0.2187)	0.0066 (0.2039)

[a]p=0.0039; [b]p=0.002; [c]p=0.008.

6.12.2: Weight z-scores at Diagnosis and Follow-up

Children with CD presented with a significantly lower weight z-score compared to UC within the overall cohort ($p<0.0001$) and among pre/early pubertal children ($p=0.0071$; table 6.12.3/6.12.4; figure 6.12.1/6.12.2). The changes in mean weight z-scores are presented in figure 6.12.1 and 6.12.2.

6.12.2.1: Crohn's Disease

There was a significant improvement in the weight z-scores from diagnosis to the first, second and fifth year in the overall cohort (table 6.12.3; figure 6.12.1). Most of the improvement was within the first year, remaining stable till the second year followed by deterioration over the next three years (figure 6.12.1; table 6.12.3).

Similar results were also found within the cohort of pre/early pubertal children. There was significant improvement in weight within the first year but then decreased between the second and fifth year following diagnosis (table 6.12.3; figure 6.12.2). Despite this, there was still a significant improvement in weight over the five years.

6.12.2.2: Ulcerative Colitis

There was a significant improvement in weight z-score within the first year in the overall cohort but then remained stable (table 6.12.4; figure 6.12.1). With regard to the pre/early pubertal children, there was an increase in the mean weight z-score between diagnosis and the first year, but this did not reach significance ($p=0.06$).

Figure 6.12.1: Temporal changes in weight z-scores (mean; standard error) in the overall cohort.

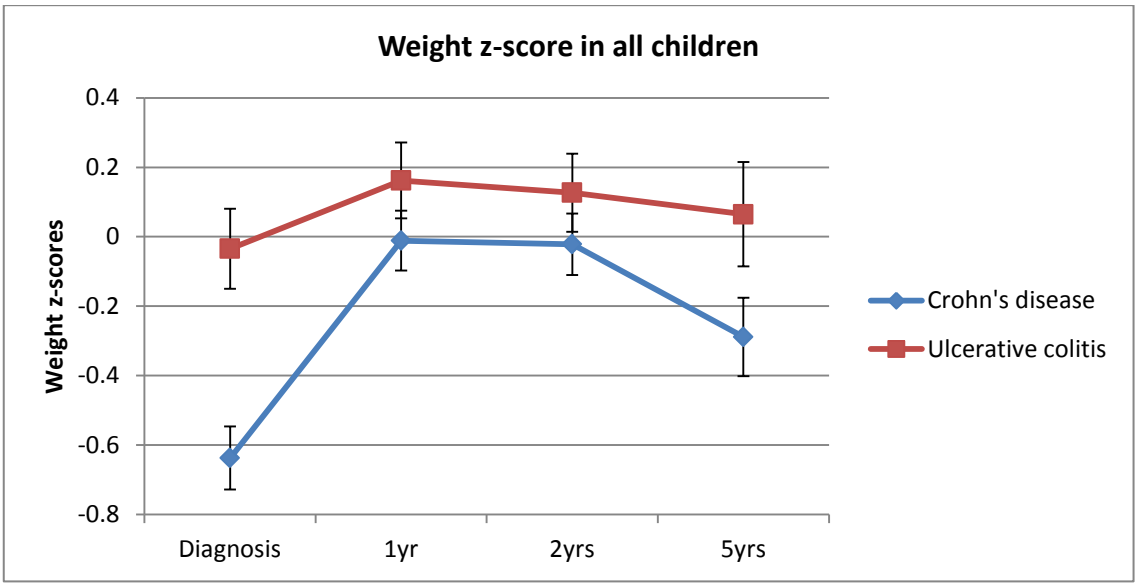
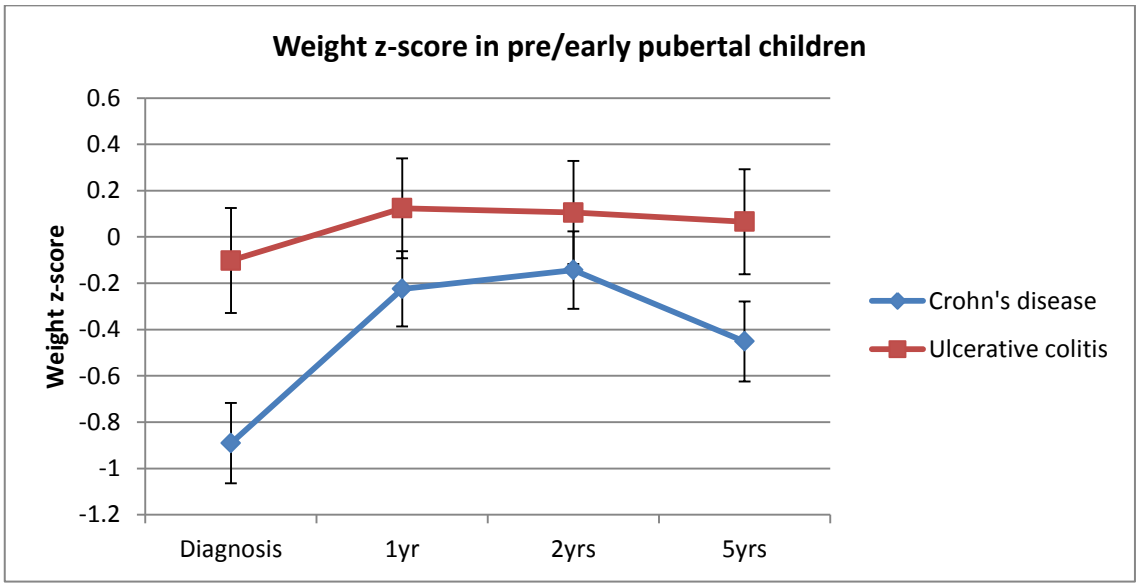


Figure 6.12.2: Temporal changes in weight z-scores (mean; standard error) of pre/early pubertal children.



6.12.3: Height z-scores at Diagnosis and Follow-up

Children with CD presented with a significantly lower mean height z-score than those with UC (p=0.0031; table 6.12.3/6.12.4; figure 6.12.3). Similar differences were found in pre/early pubertal children (p=0.0046; table 6.12.3/6.12.4; figure 6.12.4). There were no significant trends in height z-scores following diagnosis.

Figure 6.12.3: Temporal changes in height z-scores (mean; standard error) in the overall cohort.

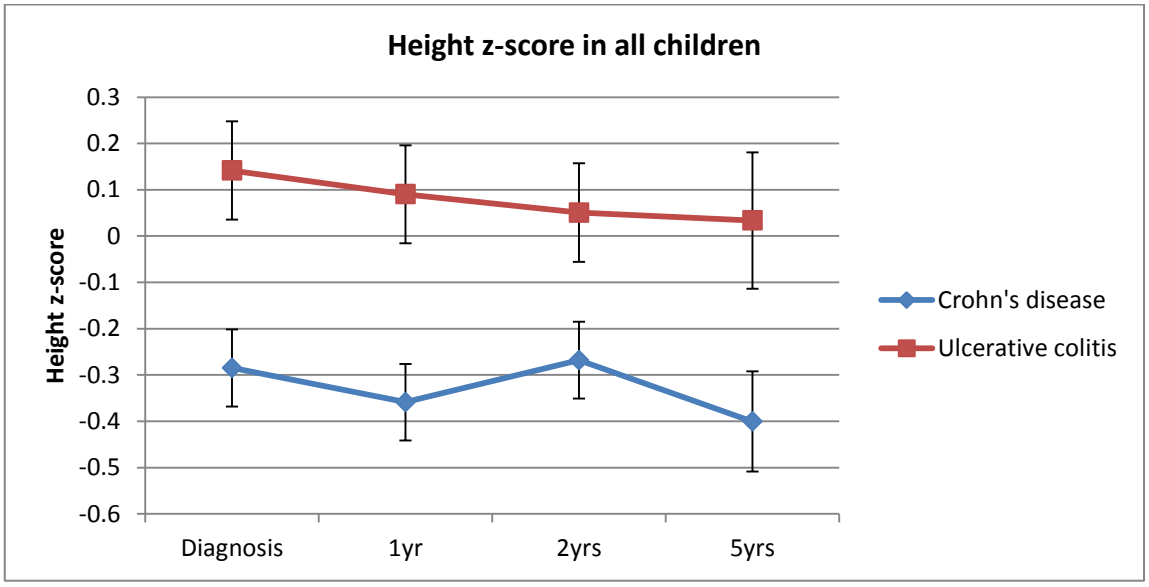
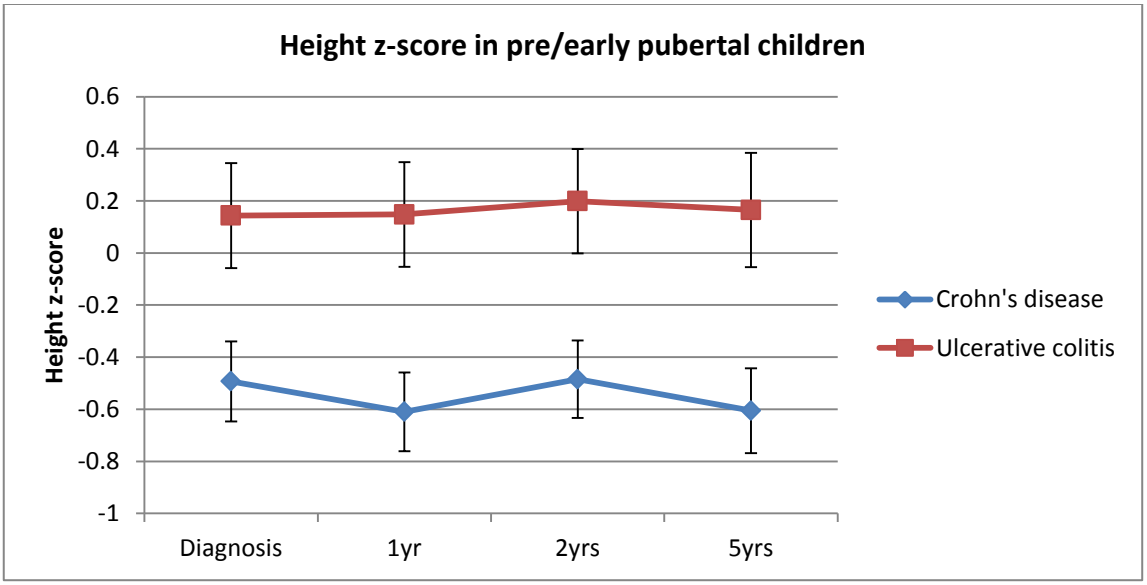


Figure 6.12.4: Temporal changes in height z-scores (mean; standard error) in pre/early pubertal children.



6.12.4: BMI z-scores at Diagnosis and Follow-up

BMI z-score at diagnosis in children with CD was worse compared to those with UC (p=0.0006; table 6.12.3/6.12.4; figure 6.12.5). There was no significant differences between the two disease subtypes at diagnosis in pre/early pubertal children (p=0.0594; table 6.12.3/6.12.4; figure 6.12.6).

6.12.4.1: Crohn's Disease

There was a significant increase in BMI z-scores within the first year following diagnosis, followed by a gradual deterioration (table 6.12.3; figure 6.12.5). The mean BMI z-score was significantly greater at one, two and five years compared to diagnosis. On the other hand, the BMI z-score was significantly lower at five years compared to the first and second year. Similar significant changes were demonstrated among the pre/early pubertal children (table 6.12.3; figure 6.12.6).

6.12.4.2: Ulcerative Colitis

Children with UC had a significant improvement in BMI z-score within the first year (table 6.12.4; figure 6.12.5). Likewise, there was an increase among pre/early pubertal children within the first year, but this had not quite reached statistical significance (p=0.051; table 6.12.4; figure 6.12.6).

Figure 6.12.5: Temporal changes in BMI z-scores (mean; standard error) in the overall cohort.

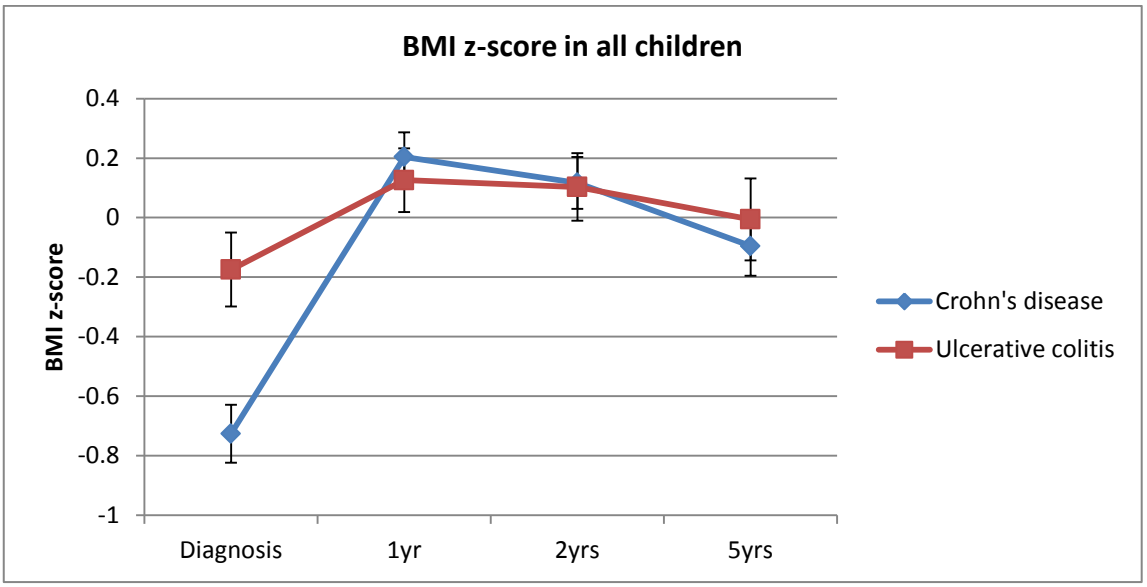
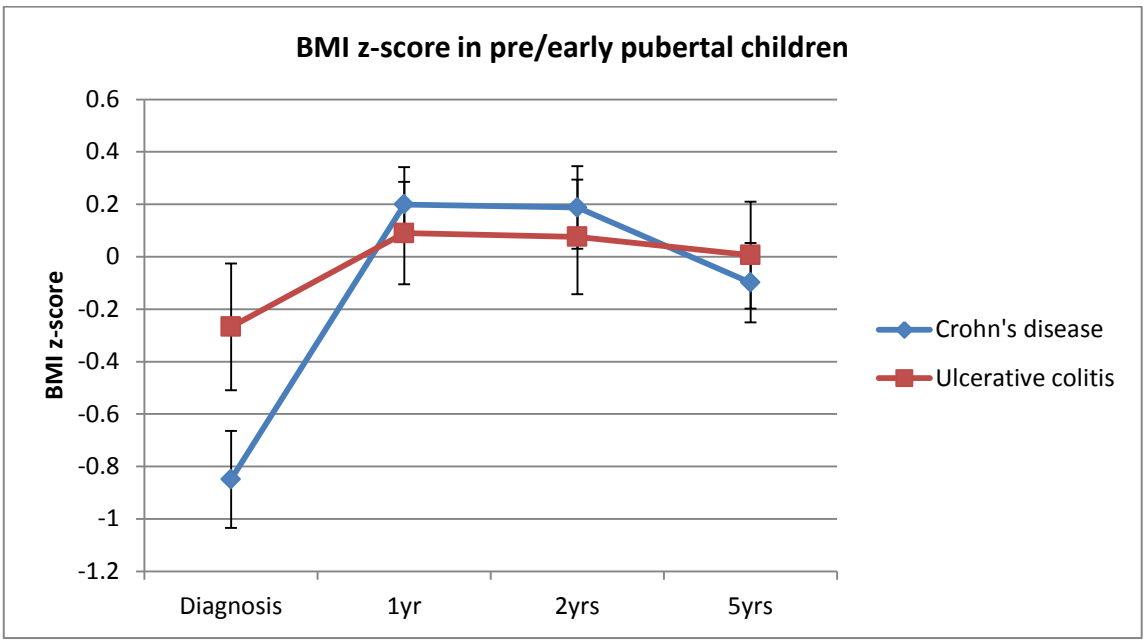


Figure 6.12.6: Temporal changes in BMI z-scores (mean; standard error) in pre/early pubertal children.



6.12.5: Predictors of Anthropometric Parameters at Diagnosis

The various predictors for diagnostic weight, height and BMI z-scores in the overall cohort and specifically among pre/early pubertal (Tanner stage 1/2) children are presented in table 6.12.5 to 6.12.10.

Table 6.12.5: Predictors for weight z-score values at diagnosis in children with CD.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall CD cohort				
Pre-diagnostic duration of symptoms (wks)	-0.005	-0.01, 0.000	0.033	164
Anal tags[a]	-0.649	-1.025, -0.272	0.001	166
Anal fissures[a]	-0.547	-0.927, -0.167	0.005	166
PCDAI score	-0.025	-0.038, -0.013	<0.001	162
Haemoglobin (g/L)	0.011	0.001, 0.021	0.038	162
Platelet (10^9/L)	-0.002	-0.003, -0.001	0.004	161
Albumin (g/L)	0.045	0.019, 0.07	0.001	154
ASCA IgA positivity	-0.765	-1.363, -0.168	0.013	64
Pre/early pubertal children with CD				
Age at diagnosis (yrs)	-0.221	-0.324, -0.118	<0.001	52
Pre-diagnostic duration of symptoms (wks)	-0.017	-0.029, -0.004	0.012	51
Anal tags[b]	-1.263	-1.996, -0.53	0.001	52
Anal fissures[b]	-1.036	-1.797, -0.275	0.009	52
Perianal abscess	-1.686	-3.347, -0.024	0.047	52
PCDAI score	-0.028	-0.053, -0.002	0.033	51
Albumin (g/L)	0.067	0.008, 0.126	0.028	48
ASCA IgA positivity	-1.037	-2.002, -0.072	0.036	31

[a]Strong correlation between anal tags and fissures at diagnosis (Pearson correlation: 0.476; 1 tailed p-value: <0.001).
[b]Strong correlation between anal tags and fissures (Pearson correlation: 0.527; 1-tailed p-value: <0.001).

Table 6.12.6: Predictors for weight z-score values at diagnosis in children with UC.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall UC cohort				
Endoscopic colitis score	-0.264	-0.447, -0.081	0.005	101
Haemoglobin (g/L)	0.01	0.002, 0.018	0.021	100
CRP (mg/L)	0.057	0.023, 0.91	0.001	95
Pre/early pubertal children with UC				
Nil				

Table 6.12.7: Predictors for height z-score values at diagnosis in children with CD.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall CD cohort				
Pre-diagnostic duration of symptoms (wks)	-0.007	-0.011, -0.003	0.002	161
Anal tags	-0.418	-0.775, -0.062	0.022	163
Ocular EIMs	-1.569	-2.887, -0.251	0.02	163
Pre/early pubertal children with CD				
Age at diagnosis (yrs)	-0.188	-0.279, -0.096	<0.001	51
Pre-diagnostic duration of symptoms (wks)	-0.018	-0.029, -0.007	0.002	50
Anal tags	-0.89	-1.563, -0.216	0.011	51
Ocular EIMs	-1.949	-3.7, -0.198	0.03	51

Table 6.12.8: Predictors for height z-score values at diagnosis in children with UC.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall UC cohort				
Albumin (g/L)	0.032	0.000, 0.064	0.049	92
Pre/early pubertal children with UC				
ESR (mm/hr)	-0.017	-0.03, -0.004	0.012	28

Table 6.12.9: Predictors for BMI z-score values at diagnosis in children with CD.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall CD cohort				
Anal tags[a]	-0.556	-0.973, -0.14	0.009	162
Anal fissures[a]	-0.814	-1.219, -0.408	<0.001	162
PCDAI score	-0.032	-0.046, -0.018	<0.001	158
Platelet count (10^9/L)	-0.002	-0.003, -0.001	0.002	157
ESR (mm/hr)	-0.009	-0.017, -0.002	0.018	155
CRP (mg/L)	-0.004	-0.007, 0.000	0.045	146
Albumin (g/L)	0.053	0.026, 0.081	<0.001	151
Ferritin (µg/L)	-0.007	-0.01, -0.003	<0.001	115
Presence of mouth ulcers either prior to or at diagnosis	-0.49	-0.942, -0.039	0.033	162
Positive first degree family history of IBD	0.771	0.091, 1.45	0.026	162
Positive ASCA IgA	-0.858	-1.504, -0.211	0.01	63
Pre/early pubertal children with CD				
Age at diagnosis (years)	-0.209	-0.324, -0.094	0.001	50
Anal tags[b]	-1.099	-1.883, -0.315	0.007	50
Anal fissures[b]	-1.041	-1.832, -0.25	0.011	50
Perianal fistula[c]	-1.473	-2.953, 0.006	0.051	50
Perianal abscess[c]	-2.043	-3.699, -0.387	0.017	50
PCDAI score	-0.044	-0.069, -0.02	0.001	49
Presence of terminal ileal disease (L1/L3)[d]	-1.020	-1.849, -0.192	0.017	47
Platelet count (10^9/L)	-0.002	-0.004, 0.000	0.032	48
ESR (mm/hr)	-0.021	-0.037, -0.006	0.008	47
WCC (10^9/L)	-0.027	-0.054, -0.001	0.043	48
CRP (mg/L)	-0.012	-0.023, 0.000	0.046	43
Albumin (g/L)	0.094	0.036, 0.151	0.002	46
Ferritin (µg/L)	-0.011	-0.017, -0.004	0.001	39
Mouth ulcers prior to or at diagnosis	-0.814	-1.627, -0.001	0.050	50
Positive ASCA IgA[d]	-1.329	-2.354, -0.304	0.013	30

[a]Strong correlation between anal tags and fissures (Pearson correlation: 0.463; 1-tailed p-value: <0.001).
[b]Strong correlation between anal tags and fissures (Pearson correlation: 0.507; 1-tailed p-value: <0.001).
[c]Strong correlation between perianal fistula and abscesses (Pearson correlation: 0.857; 1-tailed p-value: <0.001).
[d]Strong correlation between terminal ileum CD and ASCA IgA positivity (Pearson correlation: 0.509; 1-tailed p-value: 0.003).

Table 6.12.10: Predictors for BMI z-score values at diagnosis in children with UC.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size
Overall UC cohort				
Age at diagnosis (yrs)	0.055	0.002, 0.107	0.041	99
Endoscopic colitis score	-0.25	-0.439, -0.061	0.01	98
Albumin (g/L)	0.052	0.017, 0.086	0.004	92
Pre/early pubertal children with UC				
Pre-diagnosis duration of symptoms (wks)	-0.021	-0.037, -0.004	0.016	30

6.12.6: Predictors of Anthropometric Parameters in Pre/Early Pubertal Children at one, two and five years following Diagnosis

6.12.6.1: Weight z-scores following Diagnosis

6.12.6.1.1: Crohn's Disease

The weight z-score at time of diagnosis was directly associated with subsequent z-scores, whereas age at diagnosis, duration of symptoms prior to diagnosis and presence of anal tags had an inverse effect (table 6.12.11). Early introduction of azathioprine within the first 16 weeks had a favourable impact upon the weight z-score at one year when analysed with diagnostic weight z-score and corticosteroid duration (estimate: 0.458; 95% CI: 0.024, 0.893; p=0.039). Otherwise, corticosteroid duration had no influence upon subsequent weight z-scores.

Table 6.12.11: Predictors of weight z-score values at 1, 2 and 5 years following diagnosis in pre/early pubertal children with CD.

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**	**Multivariate p-value[c]**
At 1 year							
Wt z-score (entire cohort)	0.822	0.665, 0.979	<0.001	46		<0.001	<0.001
Wt z-score (females)	0.692	0.439, 0.944	<0.001	19		N/A[g]	N/A[g]
Wt z-score (male)	0.928	0.718, 1.139	<0.001	27		<0.001	N/A[g]
Age (yrs)	-0.141	-0.245, -0.037	0.009	45	N/A[d]	0.013	0.009
Pre-diagnostic duration of symptoms (wks)	-0.013	-0.025, -0.001	0.029	45	0.958	0.037	0.038
At 2 years							
Wt z-score (entire cohort)	0.789	0.596, 0.982	<0.001	42		<0.001	<0.001
Wt z-score (female)	0.531	0.236, 0.827	0.002	16		N/A[g]	N/A[g]
Wt z-score (male)	0.984	0.732, 1.235	<0.001	26		<0.001	N/A[g]
Age (years)	-0.153	-0.275, -0.031	0.015	42	N/A[e]	0.023	0.015
At 5 years							
Wt z-score (entire cohort)	0.700	0.431, 0.969	<0.001	26		<0.001	N/A[g]
Wt z-score (female)	0.406	0.073, 0.738	0.023	10		N/A[g]	N/A[g]
Wt z-score (male)	0.986	0.648, 1.323	<0.001	16		N/A[g]	N/A[g]
Anal tags	-1.287	-2.282, -0.292	0.013	27	N/A[f]	0.034	N/A[g]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic weight z-score included as an independent factor.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Multivariate analysis with early introduction of azathioprine (within the first 16 weeks) and corticosteroid duration.
[d]Strong correlation between diagnostic age and diagnostic weight z-score (Pearson correlation: -0.52; 1-tailed p-value: <0.001).
[e]Strong correlation between diagnostic age and diagnostic weight z-score (Pearson correlation: -0.467; 1-tailed p-value: 0.001).
[f]Strong correlation between the presence of anal tags and weight z-score at diagnosis (Pearson correlation: -0.441; 1-tailed p-value: 0.012).
[g]Small sample size.

6.12.6.1.2: Ulcerative Colitis

The weight at time of diagnosis was significantly associated with subsequent anthropometric parameters (table 6.12.12). A raised diagnostic ferritin level was associated with an improvement in weight at two years. In contrast, a raised diagnostic ESR was associated with a lower weight at one year, which lost significance when analysed with diagnostic weight z-score (p=0.061; table 6.10.12). The duration of corticosteroids (days) within the first five years following diagnosis was associated with a poorer weight (estimate: -0.001; 95% CI: -0.001, 0.000; p=0.036).

Table 6.12.12: Predictors for weight z-score values at 1, 2 and 5 years following diagnosis in pre/early pubertal children with UC.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size	Multivariate p-value[a]	Multivariate p-value[b]
At 1 year						
Wt z-score (entire cohort)	0.713	0.54, 0.887	<0.001	24		<0.001
Wt z-score (female)	0.672	0.327, 1.017	0.002	10		N/A[c]
Wt z-score (male)	0.737	0.504, 0.97	<0.001	14		N/A[c]
ESR (mm/hr)	-0.015	-0.027, -0.004	0.014	22	0.061	N/A[d]
At 2 years						
Wt z-score (entire cohort)	0.634	0.423, 0.845	<0.001	23		<0.001
Wt z-score (female)	0.498	0.203, 0.792	0.005	10		N/A[c]
Wt z-score (male)	0.714	0.393, 1.034	<0.001	13		N/A[c]
Serum ferritin (µg/L)	0.028	0.004, 0.051	0.026	11	N/A[c]	N/A[c]
At 5 years						
Wt z-score[e]	0.589	0.236, 0.943	0.003	16		N/A[c]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic weight z-score included as an independent predictor.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Sample size was small
[d]Analysis not possible because of the strong association between diagnostic ESR and corticosteroid duration (Pearson correlation: 0.432; 1-tailed p-value: 0.022).
[e]Analysis of diagnostic weight among females and males was not possible given the small sample size.

6.12.6.2: Height z-scores following Diagnosis

6.12.6.2.1: Crohn's Disease

The height z-score at diagnosis was directly associated with subsequent z-scores (table 6.12.13). Age at diagnosis, presence of anal tags/fissures and ocular extra-intestinal manifestations at diagnosis, and pre-diagnostic duration of symptoms was associated with poorer height z-score during the follow-up period (table 6.12.13).

Table 6.12.13: Predictors for height z-score values at 1, 2 and 5 years following diagnosis in pre/early pubertal children with CD.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size	Multivariate p-value[a]	Multivariate p-value[b]	Multivariate p-value[c]
At 1 year							
Ht z-score (entire cohort)	0.949	0.864, 1.035	<0.001	45		<0.001	<0.001
Ht z-score (female)	0.977	0.852, 1.101	<0.001	19		N/A[i]	N/A[i]
Ht z-score (male)	0.943	0.824, 1.061	<0.001	26		<0.001	N/A[i]
Age at Diagnosis (yrs)	-0.153	-0.244, -0.061	0.002	45	N/A[d]	0.003	0.001
Pre-diagnostic duration of disease (wks)	-0.018	-0.028, -0.008	0.001	45	N/A[e]	0.001	0.001
Anal tags	-0.892	-1.542, -0.241	0.008	45	0.484	0.011	0.001
Anal fissure	-0.743	-1.414, -0.072	0.031	45	0.094	0.019	0.005
Ocular EIMs	-1.799	-3.416, -0.182	0.03	45	0.75	0.039	0.049
At 2 years							
Ht z-score (entire cohort)	0.852	0.722, 0.981	<0.001	41		<0.001	<0.001
Ht z-score (female)	0.813	0.577, 1.05	<0.001	16		N/A[i]	N/A[i]
Ht z-score (male)	0.908	0.745, 1.071	<0.001	25		<0.001	N/A[i]
Age at diagnosis (years)	-0.125	-0.228, -0.023	0.018	41	N/A[f]	0.026	0.010
Pre-diagnostic duration of disease (weeks)	-0.016	-0.027, -0.005	0.008	40	N/A[g]	0.011	0.019
Anal tags	-0.736	-1.446, -0.025	0.043	41	0.602	0.059	0.017
At 5 years							
Ht z-score (entire cohort)	0.52	0.262, 0.778	<0.001	26		<0.001	N/A[i]
Ht z-score (female)	0.42	-0.082, 0.921	0.09	10		N/A[i]	N/A[i]
Ht z-score (male)	0.856	0.535, 1.177	<0.001	16		N/A[i]	N/A[i]
Pre-diagnostic duration of disease (weeks)	-0.017	-0.028, -0005	0.008	27	N/A[h]	0.01	N/A[i]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic height z-score included.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Multivariate analysis with early introduction of azathioprine (within the first 16 weeks) and corticosteroid duration.
[d]Strong correlation between diagnostic age and height z-score (Pearson correlation: -0.457;1-tailed p-value: <0.001).
[e]Strong correlation between pre-diagnosis duration of symptoms and diagnostic height z-score (Pearson correlation: -0.499; 1-tailed p-value: <0.001).
[f]Strong correlation between diagnostic age and height z-score (Pearson correlation: -0.479; 1-tailed p-value: 0.001).
[g]Strong correlation between pre-diagnostic duration of symptoms and height z-score at diagnosis (Pearson correlation: -0.454; 1-tailed p-value: 0.002).
[h]Strong correlation between pre-diagnostic duration of symptoms and diagnostic height z-score (Pearson correlation: -0.588; 1-tailed p-value: 0.001).
[i]Small sample size.

6.12.6.2.2: Ulcerative Colitis

The predictors for height z-scores in children with UC are presented in table 6.12.14. Height z-score at time of diagnosis had a significant impact upon subsequent height. Lower diagnostic haemoglobin, raised ESR, increased endoscopic colitis score and longer duration of symptoms prior to diagnosis was associated with poorer height over the follow-up period (table 6.12.14).

Table 6.12.14: Predictors for height z-scores values at 1, 2 and 5 years following diagnosis in pre/early pubertal children with UC.

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**	**Multivariate p-value[c]**
At 1 year							
Ht z-score (entire cohort)[f]	0.829	0.592, 1.066	<0.001	21		<0.001	N/A[e]
Ht z-score (male)	0.633	0.282, 0.984	0.002	13		N/A[e]	N/A[e]
Hb (g/L)	0.019	0.003, 0.034	0.019	20	N/A[d]	0.015	N/A[e]
ESR (mm/hr)	-0.016	-0.03, -0.002	0.024	19	N/A[e]	N/A[e]	N/A[e]
At 2 years							
Ht z-score (entire cohort)[g]	0.782	0.423, 1.14	<0.001	18	N/A[e]	N/A[e]	N/A[e]
Endoscopic colitis score	-0.336	-0.646, -0.027	0.035	17	N/A[e]	N/A[e]	N/A[e]
At 5 years							
Ht z-score (entire cohort)[g]	0.88	0.232, 1.527	0.012	15	N/A[e]	N/A[e]	N/A[e]
Duration of symptoms prior to diagnosis (weeks)	-0.029	-0.054, -0.004	0.026	15	N/A[e]	N/A[e]	N/A[e]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic height z-score included.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Multivariate analysis with early introduction of azathioprine (within the first 16 weeks) and corticosteroid duration.
[d]Strong correlation between diagnostic haemoglobin and diagnostic height z-score (Pearson correlation: 0.445; 1-tailed p-value: 0.025).
[e]Sample size is small.
[f]Not able to assess diagnostic height in girls because of small sample size.
[g]Not able to analyse according to gender because of small sample size.

6.12.6.3: BMI z-scores following Diagnosis

6.12.6.3.1: Crohn's Disease

It was not surprising that the BMI z-score at time of diagnosis had a direct impact upon subsequent BMI z-scores (table 6.10.15). Older age at diagnosis, higher ferritin values and ASCA positivity was associated with a poorer BMI z-score following diagnosis (table 6.10.15). Corticosteroid refractoriness during the induction period was also associated with a poorer BMI z-score at two years despite controlling for the diagnostic BMI z-score and corticosteroid duration (table 6.10.15).

Table 6.12.15: Predictors for subsequent BMI z-score values in pre/early pubertal children diagnosed with CD.

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size	Multivariate p-value[a]	Multivariate p-value[b]	Multivariate p-value[c]
At 1 year							
BMI z-score (entire cohort)	0.549	0.37, 0.728	<0.001	44		<0.001	<0.001
BMI z-score (female)	0.442	0.156, 0.727	0.005	19		N/A[i]	N/A[i]
BMI z-score (male)	0.655	0.412, 0.897	<0.001	25		<0.001	N/A[i]
Age (years)	-0.092	-0.182, -0.001	0.047	45	N/A[d]	0.067	0.094
Ferritin (µg/L)	-0.006	-0.011, -0.002	0.009	36	N/A[e]	0.015	0.034
ASCA IgA positivity	-1.265	-2.005, -0.525	0.002	26	N/A[f]	0.002	N/A[i]
ASCA IgG positivity	-1.018	-1.797, -0.238	0.013	26	0.009	0.015	N/A[i]
At 2 years							
BMI z-score (entire cohort)	0.628	0.42, 0.835	<0.001	40		<0.001	<0.001
BMI z-score (female)	0.399	0.088, 0.711	0.016	16		N/A[i]	N/A[i]
BMI z-score (male)	0.841	0.557, 1.124	<0.001	24		<0.001	N/A[i]
Age (years)	-0.139	-0.248, -0.031	0.013	41	N/A[g]	0.023	0.025
ASCA IgA positivity	-1.429	-2.382, -0.475	0.005	23	N/A[h]	0.006	N/A[i]
Corticosteroid refractoriness during induction period (vs corticosteroid responsive/ dependent)	-2.124	-3.843, -0.406	0.017	35	0.037	0.049	0.058
At 5 years							
BMI z-score (entire cohort)	0.593	0.345, 0.842	<0.001	25		<0.001	N/A[i]
BMI z-score (female)	0.339	0.097, 0.581	0.012	10		N/A[i]	N/A[i]
BMI z-score (male)	0.876	0.516, 1.236	<0.001	15		N/A[i]	N/A[i]
ASCA IgA positivity	-2.072	-3.744, -0.4	0.02	12	N/A[i]	N/A[i]	N/A[i]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic height z-score included.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Multivariate analysis with early introduction of azathioprine (within the first 16 weeks) and corticosteroid duration.
[d]Strong correlation between diagnostic age and diagnostic BMI z-score (Pearson correlation: -0.467; 1-tailed p-value: 0.001).
[e]Strong correlation between diagnostic ferritin and diagnostic BMI z-score (Pearson correlation: -0509; 1-tailed p-value: 0.001).
[f]Strong correlation between positive ASCA IgA and diagnostic BMI z-score (Pearson correlation: -0.455; 1-tailed p-value: 0.010).
[g]Strong correlation between diagnostic age and diagnostic BMI z-score (Pearson correlation: -0.419; 1-tailed p-value: 0.004).
[h]Strong correlation between positive ASCA IgA and diagnostic BMI z-score (Pearson correlation: -0.704; 1-tailed p-value: <0.001).
[i]Small sample size.

6.12.6.3.2: Ulcerative Colitis

The BMI z-score at time of diagnosis had a direct effect upon subsequent measurements (table 6.12.16). A positive first degree family history of IBD was associated with an improved BMI z-score at five years following diagnosis (table 6.12.16).

Table 6.12.16: Predictors for subsequent BMI z-score values in pre/early pubertal children diagnosed with UC.

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**	**Multivariate p-value[c]**
At 1 year							
BMI z-score (entire cohort)[e]	0.534	0.254, 0.815	0.001	21		0.001	N/A[d]
BMI z-score (male)	0.494	0.101, 0.886	0.018	13		N/A[d]	N/A[d]
At 2 years							
BMI z-score (entire cohort)[f]	0.453	0.153, 0.754	0.006	18		N/A[d]	N/A[d]
At 5 years							
BMI z-score (entire cohort)[f]	0.408	0.091, 0.724	0.016	15		N/A[d]	N/A[d]
Family history in a 1st degree relative	0.957	0.388, 1.527	0.003	15	N/A[d]	N/A[d]	N/A[d]

N/A: analysis not possible.
[a]Multivariate analysis with diagnostic BMI z-score included.
[b]Multivariate analysis with corticosteroid duration during the specified period included.
[c]Multivariate analysis with early introduction of azathioprine (within the first 16 weeks) and corticosteroid duration.
[d]Small sample size.
[e]Not analysed for girls because of small sample size.
[f]Not analysed according to gender because of small sample.

6.12.6.4: Predictors of Anthropometric Changes following Diagnosis in Pre/Early Pubertal Children

6.12.6.4.1: Weight z-scores

6.12.6.4.1.1: Crohn's Disease

The predictors for weight z-scores change within the first five years following diagnosis are presented in table 6.12.17. It was interesting to note that the diagnostic weight z-score had an inverse relationship with the magnitude of change following diagnosis, especially in females and not males (table 6.12.17). Over the five year period, males were more likely to have negative weight z-score changes compared to females (estimate: -0.749; 95% CI: -1.479, -0.019; p-value: 0.045). Children diagnosed with a higher PCDAI, endoscopic colitis score, white cell count and CRP, and/or lower haemoglobin and serum albumin were likely to have a greater improvement in weight z-score following diagnosis (table 6.12.17).

Table 6.12.17: Predictors for weight z-score change following diagnosis in pre/early pubertal children with CD.

Parameters at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size	Multivariate p-value[b]	Multivariate p-value[c]	Multivariate p-value[d]
Within the first year (change between 1st year and diagnosis)							
Wt z-score (entire cohort)	-0.178	-0.335, -0.021	0.027	45		0.031	0.055
Wt z-scores (females)	-0.308	-0.561, -0.056	0.021	18		N/A[f]	N/A[f]
Wt z-score (males)	-0.072	-0.282, 0.139	0.491	26		0.704	N/A[f]
PCDAI	0.021	0.008, 0.033	0.033	46	0.008	0.002	0.029
Endoscopic colitis score	0.183	0.044, 0.322	0.009	44	0.014	0.024	0.078
Hb (g/L)	-0.013	-0.024, -0.001	0.029	46	0.039	0.038	0.298
WCC (10^9/L)	0.000	0.000, 0.000	0.001	46	0.01	0.002	0.004
Albumin (g/L)	-0.042	-0.069, -0.014	0.003	44	0.023	0.006	0.028
Within the first 2 years (difference between 2nd year and diagnosis)							
Wt z-score (entire cohort)	-0.211	-0.404, -0.018	0.033	42		0.030	0.029
Wt z-scores (females)	-0.469	-0.764, -0.173	0.004	16		N/A[f]	N/A[f]
Wt z-score (males)	-0.016	-0.268, 0.235	0.894	26		0.98	N/A[f]
PCDAI score	0.022	0.006, 0.038	0.006	41	0.036	0.008	0.044
Endoscopic colitis score	0.211	0.034, 0.388	0.019	40	0.022	0.026	0.063
Hb (g/L)	-0.018	-0.034, -0.003	0.018	41	0.037	0.031	0.179
WCC (10^9/L)	0.000	0.000, 0.000	0.002	41	0.015	0.005	0.012
CRP (mg/L)	0.007	0.0004, 0.014	0.038	36	0.043	0.058	0.177
Albumin (g/L)	-0.053	-0.090, -0.015	0.006	39	0.042	0.009	0.023
Within first 5 years (difference between 5th year and diagnosis)							
Wt z-score (entire cohort)	-0.300	-0.569, -0.031	0.030	26		0.032	N/A[f]
Wt z-scores (females)	-0.594	-0.927, -0.262	0.0044	10		N/A[f]	N/A[f]
Wt z-score (males)	-0.014	-0.352, 0.323	0.928	16		N/A[f]	N/A[f]
WCC (10^9/L)	0.000	0.000, 0.000	0.0074	26	N/A[e]	0.036	N/A[f]

N/A: analysis not possible

[a]Multivariate analysis when controlling for gender.

[b]Multivariate analysis with the inclusion of diagnostic weight z-score.

[c]Multivariate analysis with the inclusion of systemic corticosteroid duration during the specified period.

[d]Multivariate analysis with systemic corticosteroid duration and early introduction of azathioprine included as covariates.

[e]Strong correlation between diagnostic white cell count and diagnostic weight z-score (Pearson correlation: -0.403; 1-tailed p-value: 0.021).

[f]Small sample size

6.12.6.4.1.2: Ulcerative Colitis

Weight z-score at time of diagnosis had a strong inverse impact upon subsequent anthropometric parameters (table 6.12.18). Children who were diagnosed at a better nutritional state were less likely to increase their weight z-score. Older children, those with a greater endoscopic colitis score and/or p-ANCA positivity at diagnosis were likely to undergo an improvement in their weight z-score (table 6.12.18).

Table 6.12.18: Predictors for weight z-scores changes following diagnosis in pre/early pubertal children diagnosed with UC.[*]

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**
Within the first year (difference between 1st year and diagnosis)						
Wt z-score (entire cohort)	-0.287	-0.460, -0.113	0.003	24		0.002
Wt z-score (females)	-0.328	-0.673, 0.017	0.060	10		N/A[c]
Wt z-score (males)	-0.263	-0.496, -0.030	0.030	14		N/A[c]
Age at diagnosis (yrs)	0.048	0.008, 0.087	0.032	24	0.030	0.035
Endoscopic colitis score	0.159	0.032, 0.287	0.014	23	0.073	0.021
p-ANCA positivity (positive vs negative)	0.319	0.043, 0.595	0.023	20	0.088	0.085
Within first 2 years (difference between 2nd year and diagnosis)						
Wt z-score (entire cohort)	-0.366	-0.577, -0.155	0.002	23		0.001
Wt z-score (females)	-0.502	-0.797, -0.208	0.004	10		N/A[c]
Wt z-score (males)	-0.286	-0.607, 0.034	0.075	13		N/A[c]
Within first 5 years (difference between 5th year and diagnosis)						
Wt z-score (entire cohort)	-0.411	-0.764, -0.057	0.027	16		N/A[c]
Wt z-score (females)	-0.172	-0.790, 0.445	0.531	9		N/A[c]
Wt z-score (males)	-0.502	-1.177, 0.174	0.114	7		N/A[c]

N/A: analysis not possible
[a]Multivariate analysis with the inclusion of diagnostic weight z-score.
[b]Multivariate analysis with the inclusion of systemic corticosteroid duration during the specified period.
[c]Small sample size.
[*]Multivariate analysis with duration of systemic corticosteroids and early use of azathioprine was not possible given that the sample size was less than 30.

6.12.6.4.2: Height z-scores

6.12.6.4.2.1: Crohn's Disease

The height z-score at time of diagnosis was the only predictor of subsequent changes in the z-score within the first two and five years (table 6.12.19).

Table 6.12.19: Predictors of change in height z-scores in pre/early pubertal children diagnosed with CD.

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**
Within first 1yr (difference between 1st year and diagnosis)						
Nil predictors						
Within first 2 years (difference between 2nd year and diagnosis)						
Ht z-score (entire cohort)	-0.148	-0.278, -0.019	0.026	41	0.023	0.010
Ht z-score (females)	-0.187	-0.423, 0.050	0.112	16	N/A[c]	N/A[c]
Ht z-score (males)	-0.092	-0.255, 0.071	0.255	25	0.309	N/A[c]
Within first 5 years (difference the 5th year and diagnosis)						
Ht z-score (entire cohort)	-0.305	-0.573, -0.037	0.027	26	0.038	N/A[c]
Ht z-score (females)	-0.58	-1.082, -0.079	0.028	10	N/A[c]	N/A[c]
Ht z-score (males)	-0.144	-0.465, 0.177	0.353	16	N/A[c]	N/A[c]

N/A: analysis not possible.
[a]Multivariate analysis with corticosteroid duration during the specified period.
[b]Multivariate analysis with corticosteroid duration during the specified period and early use of azathioprine.
[c]Small sample size

6.12.6.4.2.2: Ulcerative Colitis

Higher PUCAI score and longer duration of symptoms prior to diagnosis was associated with decreasing height z-scores within two and five years respectively on univariate analysis (table 6.12.20).

Table 6.12.20: Predictors of change in height z-scores in pre/early pubertal children diagnosed with UC.*

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**
Within the first year (difference between 1st year and diagnosis)				
Nil predictors				
Within the first 2 years (difference between 2nd year and diagnosis)				
PUCAI score	-0.0346	-0.0674, -0.0017	0.039	18
Within first 5 years (difference between 5th year and diagnosis)				
Duration of symptoms prior to diagnosis (weeks)	-0.0325	-0.0613, -0.0037	0.0272	14

*Multivariate analysis not possible given the small cohort.

6.12.6.4.3: BMI z-scores

6.12.6.4.3.1: Crohn's Disease

There were several clinical and laboratory factors at diagnosis associated with changes in BMI z-scores following diagnosis (table 6.12.21 in Appendix C). Children diagnosed with a poorer BMI z-score were more likely to have positive improvement following diagnosis. Other factors associated with a positive change included a higher diagnostic PCDAI, endoscopic colitis score, WCC, ESR, CRP, and the presence of perianal fistula and/or abscess. The diagnostic haemoglobin and albumin was inversely associated with BMI z-score changes. Children presenting with inflammatory behaviour (B1) were more likely to have negative changes in their BMI z-score, independent of their diagnostic BMI.

6.12.6.4.3.2: Ulcerative Colitis

BMI z-score at time of diagnosis had an inverse impact upon subsequent changes in BMI (table 6.12.22). The severity of the endoscopic features was directly associated with improvement, but not when the diagnostic BMI z-score was included in the analysis (table 6.12.22). Children presenting with a higher haemoglobin or ferritin were more likely to experience deterioration in their BMI over time (table 6.12.22).

Table 6.12.22: Predictors of change in BMI z-scores in pre/early pubertal children diagnosed with UC.[*]

Predictors at Diagnosis	Estimate	95% Confidence interval	p-value	Sample size	Multivariate p-value[a]	Multivariate p-value[b]
Within the first year (difference between 1st year and diagnosis)						
BMI z-score (entire cohort)	-0.466	-0.746, -0.185	0.003	21		
BMI z-score (males)	-0.506	-0.899, -0.114	0.016	13		
Endoscopic colitis score	0.271	0.035, 0.508	0.025	20	0.148	
Hb (g/L)	-0.014	-0.027, -0.001	0.031	20	N/A[c]	
Ferritin (mcg/L)	-0.011	-0.019, -0.001	0.025	11	N/A[d]	N/A[d]
Within first 2 years (difference between 2nd year and diagnosis)						
BMI z-score (entire cohort)	-0.547	-0.847, -0.246	0.001	18		N/A[d]
Within first 5 years (difference between 5th year and diagnosis)						
BMI z-score (entire cohort)	-0.592	-0.909, -0.276	0.001	15		N/A[d]

N/A: Analysis not possible.
[a]Multivariate analysis with the inclusion of diagnostic BMI z-score.
[b]Multivariate analysis with the inclusion of systemic corticosteroid duration during the specified period.
[c]Strong correlation between diagnostic haemoglobin and diagnostic BMI z-score (Pearson correlation: 0.438; 1-tailed p-value: 0.027).
[d]Small sample size.
[*]Multivariate analysis with duration of systemic corticosteroids and early introduction of azathioprine was not possible given the small sample size.

6.12.6.5: Impact of Systemic Corticosteroid Duration and Early Azathioprine Use

Systemic corticosteroid duration and early introduction of azathioprine within the first 16 weeks had no impact upon changes in weight, height and BMI z-scores among pre/early pubertal children with CD or UC within the first five years following diagnosis.

6.12.7: Discussion of Anthropometric Data

6.12.7.1: Significant Impairment in Diagnostic Anthropometric Parameters in Children with Crohn's disease

South Australian children diagnosed with CD presented with a significantly lower weight, height and BMI z-scores compared to those with UC (table 6.12.3, 6.12.4; figure 6.12.1, 6.12.3, 6.12.5). A similar difference was found in pre/early pubertal children, except in the case of BMI z-scores where there was no significant difference (table 6.12.3, 6.12.4; figure 6.12.2, 6.12.4, 6.12.6). This result was in keeping with other studies in which anthropometric parameters at diagnosis were worse in children with CD compared to UC (table 6.12.23). [11, 70, 150, 183, 197, 198, 203-206, 208-214]

Table 6.12.23: Anthropometric parameters at time of diagnosis in children with IBD compared to international studies.[11, 70, 150, 183, 197, 198, 203-206, 208-214]

Parameter	South Australian CD children	International CD cohorts (mean range)	South Australian UC children	International UC cohorts (mean range)
Weight for age z-score	-0.637	-1.14 to -0.26	-0.034	-0.32 to 0.2
BMI for age z-score	-0.726	-1.37 to -0.66	-0.175	-0.2 to 0.024
Height for age z-score	-0.285	-1.11 to -0.28	0.142	-0.15 to 0.6

6.12.7.2: Trend in Anthropometrics following Diagnosis

6.12.7.2.1: Crohn's Disease

6.12.7.2.1.1: Weight and BMI

There was an overall improvement in both weight and BMI z-scores in children with CD (table 6.12.3; figure 6.12.1/6.12.2). Most of the increase occurred within the first year following the initiation of therapy, with no further improvement thereafter. As the disease entered clinical remission, there was decreased inflammation with decreased energy requirement, improved oral intake and decreased malabsorption. This improvement in weight and BMI z-scores was also demonstrated in other studies.[206, 210, 325] In the study by Spray et al,[206] there was a significant improvement in weight for height z-scores from -1.0 to 1.1 within three months following the initiation of therapy. In another study, children who were

diagnosed with significantly lower BMI z-scores compared to healthy controls underwent an improvement following diagnosis with the introduction of therapy such that within two years their BMI was no different to healthy children.[209]

The deterioration between the second and fifth year following diagnosis may give the impression of worsening in disease control, however, several factors may have contributed to this false interpretation. Firstly, the number of children followed at five years was lower than that at two years (table 6.12.1). Secondly, most of the children followed at five years may have been those with relapsing or medically resistant disease who required ongoing medical review. In comparison, children with well controlled CD may have been lost to follow-up. Given that this study was a retrospective case-notes review, these children were not contacted to assess their nutritional state.

6.12.7.2.1.2: Height

It was interesting that the mean height z-scores for pre/early pubertal children remained unchanged following diagnosis (table 6.12.3). The medical and/or surgical therapy had no impact upon height z-scores which was unlike the case with weight and BMI. These results were in keeping with other studies.[183, 209, 210, 216, 325] The height z-score had not changed in children within the first two and six years following diagnosis in the studies by Sylvester et al[209] and Vasseur et al[210] respectively. In contrast, Griffiths et al[217] demonstrated that the height z-score improved by 0.35 over four years in pre/early pubertal children. In the study by Pfefferkorn et al,[213] pre/early pubertal children with CD demonstrated an increased mean height velocity within the first two years following diagnosis (-0.71 to 0.26) but their final mean height z-score (-0.46) was no different to that at diagnosis (-0.49). Similar results were found in the Scottish study by Malik et al.[216] It could be interpreted that initiation of therapy in children with CD may increase the height velocity z-score during puberty, but the magnitude may still be suboptimal compared to healthy children.

Thus, the current therapy utilised in South Australian children has not corrected their height deficits within the first two years. The results may have been different if there was a larger cohort followed for a longer period, and all children were reviewed even if their disease was under good control.

The final adult height of children with CD was not assessed in the current study. Several studies have demonstrated that the final adult height was suboptimal compared to the normal population or predicted mid-parental height.[146, 204, 211, 217, 346-348] Moreover, 37 to 88% of children with CD will have deficits in their height at adulthood.[346, 347, 349]

6.12.7.2.2: Ulcerative Colitis

Children with UC demonstrated a significant increase in weight and BMI z-scores within the first year following diagnosis, but not among pre/early pubertal children (table 6.12.4). This was not surprising given the fact that children with UC generally presented with no impairment of their anthropometrics compared to healthy children.[11, 50, 67, 70, 183, 197, 204-206, 212, 218] Thus, children with UC are less likely to have growth problems following diagnosis and usually attain normal adult height.[204, 221, 348, 349] The development of weight, height and BMI issues following diagnosis may indicate that the child has CD instead of UC, and so reassessment may need to be undertaken.[17]

6.12.7.3: Predictors of Anthropometric Parameters at Diagnosis

6.12.7.3.1: Crohn's Disease

6.12.7.3.1.1: Weight and BMI z-scores at Diagnosis

There were several predictors for lower weight and BMI z-scores at diagnosis (table 6.12.5; 6.12.9). The association between older age and lower weight and BMI z-scores in pre/early pubertal children was explained by the fact these children have a marked delay in their puberty. This meant that their growth would be restricted compared to the younger children. A prolonged duration of disease prior to diagnosis and initiation of therapy may impact upon the weight but not the BMI z-score at diagnosis. There was no gender difference within this cohort. In contrast, two other paediatric studies have shown that females presented with a lower mean weight z-score compared to males.[70, 210]

Increased disease activity as measured by the PCDAI and worsened laboratory parameters was associated with lower anthropometric parameters at diagnosis. Likewise, Vasseur et al[210] demonstrated that children presenting with a CRP of greater than 10mg/L had a worsened BMI z-score.

The presence of terminal ileal disease at diagnosis was associated with a significantly reduced BMI z-score at diagnosis (table 6.12.9). Similarly, Sawczenko et al[70] demonstrated that the presence of jejunal and/or ileal disease was associated with a reduced weight z-score.

Within this South Australian cohort, there was an association between perianal lesions and poor weight/BMI z-scores at diagnosis, which has not been previously described in the literature (table 6.12.5; 6.12.9).

The association between ASCA IgA positivity and lower weight and BMI z-scores was interesting (table 6.12.5; 6.12.9). One other study has demonstrated that ASCA IgA and/or IgG positivity was associated with significantly lower weight z-scores at diagnosis, despite there being no association with extent of intestinal disease.[215]. The lack of an association with ASCA IgG positivity in this South Australian study could be related to the low number of children in whom serology was measured.

6.12.7.3.1.2: Height z-scores at diagnosis

Two other studies have demonstrated that the increased duration of symptoms prior to diagnosis was inversely associated with height z-score at diagnosis (table 6.12.7).[70, 206, 211] The presence of anal tags and ocular extra-intestinal manifestations having a negative impact upon growth has not been previously described (table 6.12.7). Anatomical distribution of disease had not influenced diagnostic height in the South Australian cohort, unlike two previous studies demonstrating that disease in the oesophagus, jejunum and/or ileum had a negative impact.[70, 214]

6.12.7.3.2: Ulcerative Colitis

There were a smaller number of predictors of anthropometric z-scores in children with UC compared to those with CD, especially in the pre/early pubertal group (table 6.12.6/6.12.8/6.12.10). The endoscopic colitis score was inversely associated with weight/BMI parameters at diagnosis in the overall cohort, reflecting a more severe disease process with increased malabsorption.

6.12.7.4: Predictors of Weight and BMI changes following Diagnosis

6.12.7.4.1: Impact of Diagnostic Anthropometric Parameters

This study reinforced the fact that the initial weight, height and BMI z-scores at time of diagnosis has a direct impact upon subsequent parameters and an inverse relationship with the magnitude of the change in both CD and UC (table 6.12.11-6.12.22).

It was not surprising that children presenting with lower anthropometrics were more likely to have impaired growth within the first five years, despite the impact of systemic corticosteroids and early use of azathioprine. In a study from Northern France of paediatric CD, children diagnosed with lower anthropometrics were more likely to have significant deficits during the disease course.[210] British children with CD who presented with minimal height deficits attained a better adult height.[211] The relationship between anthropometric parameters at diagnosis and follow-up values was significant in both females and males.

The inverse association between anthropometric parameters at diagnosis and the magnitude of change was not surprising. Children presenting with normal anthropometrics were less likely to show further increases compared to those with marked deficits who have the potential for improvement following initiation of therapy. Within the CD cohort, this association was limited to the females (table 6.12.17-6.12.22). Several studies have demonstrated that following the diagnosis of CD, females were more likely to demonstrate improvement in weight and height.[124, 210, 217, 348, 350]

6.12.7.4.2: Crohn's Disease

6.12.7.4.2.1: Weight/BMI z-scores

The older pre/early pubertal children not only presented with poorer weight and BMI z-scores, they continued to have impaired nutritional parameters during the first two years following diagnosis despite the BMI z-score rise (table 6.12.5; 6.12.9; 6.12.11; 6.12.15). This was not surprising given that such children have delayed puberty with impaired parameters.

The inverse association between the duration of symptoms prior to diagnosis with weight z-score at one year was confounded by the diagnostic weight (table 6.12.11). When analysed whilst controlling for the diagnostic weight, the above significant association was lost.

There were no gender differences with regard to weight and BMI z-scores at diagnosis and during the follow-up period. In contrast, a Northern French study by Vasseur et al,[210] demonstrated that females presented with poorer weight at diagnosis but then underwent significant improvement over the period of six years compared to the males who demonstrated no improvement. The relationship between the diagnostic weight and BMI with the magnitude of change was only present in females and not the males within the South Australian cohort (table 6.12.17; 6.12.21).

Children who were ASCA IgA positive at diagnosis were more likely to have lower BMI z-score at the specified review period of one, two and five years following diagnosis (table 6.12.15). In contrast, there were no association with intestinal disease involvement (L1-3). Similarly, the study by Trauernicht and Steiner[215] demonstrated a significant association between ASCA positivity and lower weight z-scores at diagnosis, but no relationship with intestinal disease extent. Impact of ASCA positivity on subsequent weight and BMI z-scores has not been reported previously.

There were several clinical and laboratory markers at diagnosis associated with positive change in weight and BMI z-scores (table 6.12.17; 6.12.21). These included high PCDAI, low haemoglobin, raised white cell count, low albumin, raised CRP and raised ESR (table 6.12.17; 6.12.21). It was interesting to note that PCDAI, haemoglobin, white cell count, albumin and CRP were independently associated with the magnitude of change in the weight z-score, independent of the diagnostic weight (table 6.12.17). With regard to the change in BMI z-score, a raised diagnostic white cell count was the only significant independent predictor in the multivariate analysis when controlling for the diagnostic BMI (table 6.12.21). It would appear that the degree of inflammation at diagnosis may influence subsequent change in the weight.

The presence of inflammatory behaviour (B1) was associated with a negative change in BMI z-score following diagnosis within the first five years (table 6.12.21).

6.12.7.4.2.2: Height z-scores

The duration of symptoms prior to diagnosis was inversely related to the subsequent height z-score at one, two and five years following diagnosis (table 6.12.13). Multivariate analysis with the initial height z-score was not possible given the strong correlation (table 6.12.13). It

has been shown in two other studies that the duration of disease prior to diagnosis has a negative impact upon the diagnostic height, but its relationship with subsequent change has not been reported.[70, 206, 211]

6.12.7.4.3: Ulcerative Colitis

There were several predictors of anthropometric parameters at the specified time points and the magnitude of change, including duration of symptoms prior to diagnosis, first degree family history of IBD, diagnostic age, PUCAI, haemoglobin, ESR, ferritin and p-ANCA positivity (table 6.12.12; 6.12.14; 6.12.16; 6.12.18; 6.12.20; 6.12.22). These relationships were not consistently identified at the various time points, which may be due to the small sample size. Thus, these diagnostic parameters need to be investigated in a larger study before considered as significant predictors. No other studies have investigated potential contributors towards anthropometric parameters at both diagnosis and during disease course in children with UC.

6.12.8: Limitation

The small population size during the follow-up period did have an impact upon possible associations and inability to undertake certain statistical analysis. The number of children with case note details beyond the first two years following diagnosis decreased dramatically from 278 at diagnosis and 214 at two years to 101 at five years (table 6.12.1). The number was less when the pre/early pubertal population was selected. This drop-off was due to children who were lost to follow-up or may have transitioned to adult care. It could be hypothesized that such children may have undergone sustained clinical remission and not attended further appointments. Thus, this may explain the worsening anthropometric parameters at five years, since the population may have been biased towards those with medically resistant and/or complicating disease (table 6.12.1-6.12.6). To avoid this bias, such participants should have been contacted and asked to get their weight and height recorded.

Recording of Tanner stage was done poorly since only 38.1% of the children had such details documented in the database or case notes. Tanner staging, bone age and other measures of puberty such as peak height velocity and menarche in females are important and need to be recorded as part of routine practice. In addition, a cohort of healthy children of similar bone age should have been included for comparison in this study, which was not possible given its retrospective nature.

6.12.9: Conclusion

This retrospective case note review has highlighted several interesting points with regard to growth in children with IBD. Children with CD presented with impaired anthropometric parameters, which then improved within the first year with regard to weight and BMI, but not the height z-score. This lack of improvement in height may reflect the failure of current therapy to achieve optimal outcomes. The anthropometric parameters at time of diagnosis strongly influence subsequent growth, stressing the importance of diagnosing children early and addressing their growth from the outset. Finally, several factors have been identified that influence both anthropometric values at diagnosis and subsequent growth which need to be replicated in larger prospective studies. If these factors remain significant during follow up, then their presence should influence the choice of therapy to optimise disease control and subsequent growth.

6.13: Mortality

Within this IBD cohort there were two deaths, both of whom were male and diagnosed with CD. One child was diagnosed at 17.5 years of age with inflammatory colonic disease (L2; B1). He was noncompliant with his medications and medical follow-up, requiring a proctocolectomy with resection of the terminal ileum two years following diagnosis. He died six months later (2.5 years following diagnosis) with overwhelming sepsis. The second child was diagnosed at seven years of age with ileocolonic disease and upper gastrointestinal involvement (L3+4; B1). He presented with a terminal ileal stricture just over two years following diagnosis for which he required an ileocaecal resection. Five days later, he developed septic shock and had a cardiac arrest secondary to an anastomotic leak with faecal peritonitis. Despite a Hartmann's procedure with repair of the anastomosis and drainage of abscesses, antibiotic therapy and inotropic support, he died two days later with multi-organ failure and severe cerebral oedema.

6.14: Conclusion on Disease Course in Children with Inflammatory Bowel Disease

This project was an attempt to describe the disease course in children with inflammatory bowel disease. Inflammatory bowel disease is a heterogeneous condition with regard to not only aetiology and phenotype at diagnosis, but also disease course. Thus, there is no single significant parameter that best describes the disease history. To complicate matters, children have other issues related to growth which may be affected by their disease.

Description of disease course in this study was undertaken by means of clinical symptoms, anatomical disease extent and behaviour, systemic corticosteroid use, hospitalisation, need for major surgery, growth and mortality. One of the problems with some of these parameters was the lack of a uniform definition among the limited number of published studies. Thus, a clear definition was attempted and the disease history was described within the first five years following diagnosis.

The retrospective nature of the study is typically bedevilled by missing or incomplete data. Perhaps, there are other important indicators of disease that have not been addressed given the time frame of the study and its retrospective nature, such as lean body mass accumulation, bone mineralisation/density, pubertal development, duration of school absenteeism, education level attained, psychosocial impact upon the patient and family, financial impact upon the family, relationship with other children/adolescents, future sexual relationships and family, reproduction potential and attained employment with its financial implications. These are equally important and need to be considered in any follow-up review of patients with inflammatory bowel disease.

Chapter 7: Contribution to Current Literature (Overall Conclusion)

The aim of this project was to describe the diagnostic phenotype of Australian children with inflammatory bowel disease, epidemiology within South Australia and attempt to describe disease course according to various clinical parameters. The goal of management should be assessing children according to disease severity so that therapy, whether medical or surgical, could be tailored to optimise control of inflammation and improve their overall health.

There has not been any previous work describing disease phenotype of Australian children with inflammatory bowel disease on a national scale with such a large cohort as the APAIBD database. It has been shown that Australian children presented with a similar disease extent and behaviour to those children from international cohorts. Age-related changes in disease subtype and extent in both Crohn's disease, ulcerative colitis and inflammatory bowel disease unclassified were similar to those from the Northern hemisphere, highlighting potential differences in inflammation among younger children, adolescents and adults.

New associations among the various disease phenotypic features have been identified. Presence of orofacial and perianal Crohn's disease highlighted a unique disease presentation which has not been described previously, given that other databases have been hindered by a small population size. The relationship between orofacial, perianal lesions (more specifically tags and fissures), oesophageal inflammation, dermatological and ocular extra-intestinal manifestations would suggest a distinct type of disease. This study has highlighted that there is a clear distinction between anal tags/fissures and perianal fistula/abscess, given their differing associations. Relationship between the various extra-intestinal manifestations identified in Australian children provides further understanding of such lesions and possibly similar underlying pathophysiology. Important factors influencing anthropometric parameters at diagnosis were further explored in this project.

An attempt was undertaken to describe disease follow-up in various ways. The traditional means of assessing activity according to symptoms was imprecise and ignorant of the wider impact upon the child's health. By defining the various disease parameters, and then describing the course, this will hopefully lead to further discussion and uniformity in definition, so that comparison among various studies will be possible.

Among the selected parameters, the aim of inducing mucosal healing and/or histological remission was of utmost importance, as previous studies have demonstrated a reduction in the duration of hospitalisation and corticosteroid use, and a reduction in surgical resection rates. The more worrying aspect found in the current study was the minimal impact upon the height of pre/early pubertal children following diagnosis which has been demonstrated in previous studies, highlighting the inadequacy of current therapy.

This is the first study to assess disease course according to several outcome measures, which were not complete, highlighting the complexity of inflammatory bowel disease. Other parameters, not examined in this project given its retrospective nature, but equally important include duration of school absentee, highest education achieved, body image, bone mineralisation, pubertal development, social relationships, fertility, future employment and psychological impact upon the child , parents and siblings. All these factors need to be reviewed during follow-up, hopefully improving the health of children and teenagers.

In summary, this project has improved the understanding of the uniqueness of paediatric onset inflammatory bowel disease. It has allowed an in depth discussion about various disease course parameters with its associated impact upon a child's health. Further research is needed to clarify these issues but hopefully this current project has begun this process.

Appendix A

Table 4.2: Paediatric CD activity index (PCDAI).

	Score
History (recall, one week)	
Abdominal pain	
None	0
Mild: brief; does not interfere with activities of daily living (ADL)	5
Moderate/severe: daily, nocturnal, longer lasting, affects ADL	10
Stools per day	
0-1 liquid, no blood	0
≤ 2 semi-formed and small amount of blood or 2-5 liquid	5
≥ 6 liquid stools, gross blood or nocturnal diarrhoea	10
Patient functioning, general well-being (recall, one week)	
Well with no limitations of activities	0
Below par with occasional difficulty in maintaining age appropriate activities	5
Very poor with frequent limitation of activities	10
Examination	
Weight	
Weight gain or voluntary weight stable/loss	0
Weight loss of < 10% or involuntary stable	5
Weight loss of ≥ 10%	10
Height (diagnosis)	
< 1 channel decrease from previous percentile	0
1 to < 2 channel decrease from previous percentile	5
≥ 2 channel decrease from previous percentile	10
Or	
Height velocity	
≤ -1 standard deviation from normal	0
-1 to < -2 standard deviation from normal	5
≥ -2 standard deviation from normal	10
Abdomen	
No tenderness or masses	0
Tenderness or mass without tenderness	5
Tenderness, involuntary guarding, definite mass	10
Perirectal disease	
None, asymptomatic tags	0
1-2 indolent fistula, scant drainage, no tenderness	5
Active fistula, drainage, tenderness or abscess	10
Extra-intestinal*	
None	0
1 manifestation	5
≥ 2 manifestations	10
Laboratory	
Haematocrit (%)	
6-10yrs of age (males/females): ≥33 11-19yrs of age (females): ≥34	0

11-14yrs of age (males): ≥35 15-19yrs of age (males): ≥37	
6-10yrs of age (males/females): 28-32 11-19yrs of age (females): 29-33 11-14yrs of age (males): 30-34 15-19yrs of age (males): 32-36	2.5
6-10yrs of age (males/females): <28 11-19yrs of age (females): <29 11-14yrs of age (males): <30 15-19yrs of age (males):<32	5
ESR (mm/hr)	
< 20	0
20-50	2.5
>50	5
Albumin (g/L)	
≥35	0
31-34	5
≤30	10

*Extra-intestinal includes fever of >38.5^{o}C on 3 days over the last week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum.

PCDAI activity score:

- ≤10 (no activity)
- 11-30 (mild activity)
- >30 (moderate-severe activity)

Appendix B

AUSTRALIAN PAEDIATRIC AND ADOLESCENT IBD DATA BASE

FIRST NAME: ☐☐ **SURNAME:** ☐☐

(First two letters e.g. James=JA) *(First two letters)*

Date of birth: _____ **Sex:** ____ **State** residing in at diagnosis (circle): NSW, NT, QLD, SA, TAS, WA, VIC

Current post code: ☐☐☐☐ Postcode at **time of diagnosis** (if different)**:** ☐☐☐☐

Dr in charge**:** _____ Dr's email address update: _____

Follow up Dr if differs from above: _____ **Hospital** where care based:

_____

Date of **Diagnosis:** _____

Duration of symptoms prior to diagnosis in weeks/months specify: _____

PRESENTATION DATA

A. DIAGNOSIS:

Tick diagnosis - one only *(definition: refer to key attached)*

☐ Crohn's disease
☐ Ulcerative colitis
☐ Indeterminate colitis

B. EXTENT & SEVERITY OF INTESTINAL INVOLVEMENT AT DIAGNOSIS:

Grade: Grade of severity of colitis *(refer key attached)*

If severity of Pancolitis non-uniform, record grade of involvement of each colonic segment.

Indicate areas involved

Yes	No		Grade of colitis (see key below)	Eosinophils prominent Tick Yes	Eosinophils prominent Tick No	Eosinophils prominent Tick ?	Granuloma Present Yes	Granuloma Present No	Granuloma Present ?
☐	☐	Orofacial (other than aphthous ulcers)					☐	☐	☐
☐	☐	Oesophagus							
☐	☐	Stomach					☐	☐	☐
☐	☐	Duodenum							
☐	☐	Jejunum							
☐	☐	Ileum (excluding TI)							
☐	☐	Terminal Ileum					☐	☐	☐
☐	☐	Appendix					☐	☐	☐
☐	☐	Caecum	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Ascending Colon	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Transverse Colon	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Descending Colon	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Sigmoid Colon	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Rectum	[ ]	☐	☐	☐	☐	☐	☐
☐	☐	Pancolitis	[ ]	☐	☐	☐	☐	☐	☐

Yes No

☐ ☐ **Perianal Disease**
If yes, indicate: ☐Anal Fissure(s), ☐Abscess ☐Anal Tag(s), ☐Ulcer

☐ ☐ **Fistula(e) any site**
If yes, describe _____

☐ ☐ **Stricture/stenosis, any site**
If yes, describe _____

☐ ☐ **Abscess or collection** (eg pararectal, TI)
If yes, describe _____

Yes No

☐ ☐ **UGIE at Diagnosis**

☐ ☐ **Colonoscopy at Diagnosis**

If Yes, colonoscopy to:

☐ Terminal ileum ☐ Caecum

☐ Hepatic flexure ☐ Splenic flexure

☐ Sigmoid colon ☐ Rectum

EXTRAINTESTINAL INVOLVEMENT AT DIAGNOSIS (ONCE WORKUP COMPLETED)

Yes No

☐ ☐ **Hepatobiliary Involvement**

If Yes - tick diagnosis:

- ☐ Sclerosing cholangitis
- ☐ Pericholangitis
- ☐ Chronic active hepatitis
- ☐ Cholelithiasis
- ☐ Fatty liver
- ☐ Liver abscess
- ☐ Undiagnosed (elevated enzymes only)

Yes No

☐ ☐ **Eye abnormality**

If Yes - Tick diagnosis

- ☐ Iritis
- ☐ Uveitis
- ☐ Red eye (s) NYD
- ☐ Other (describe) _____

Yes No

☐ ☐ **Arthropathy**

If Yes - Tick diagnosis

- ☐ Arthritis
- ☐ Arthralgia
- ☐ Spondylitis
- ☐ Enthysitis
- ☐ Other (describe) _____

Yes No
☐ ☐ **Skin** (include history of involvement)
If Yes - Tick Diagnosis:
☐ Erythema nodosum
☐ Pyoderma gangrenosum
☐ Vasculitic rash
☐ Other (describe) _____

Yes No
☐ ☐ **Mouth ulcers** (aphthous, include history of)
Yes No
☐ ☐ **Pulmonary**
If Yes, describe _____

Yes No
☐ ☐ **Other**
If Yes, describe _____

D. EPIDEMIOLOGY

Country of Birth of Patient:
☐ Australia
☐ Other (specify):_____

Racial Origin(s) <u>Mother</u>:
☐ Caucasian
☐ Jewish ☐ Indian subcontinent
☐ Asian
☐ Chinese ☐ SE Asian
☐ Other (specify) _____
☐ Aboriginal
☐ Mixed (specify):_____
☐ Other (specify): _____
☐ Unknown
Ethnic Origin Mother (eg Italian, German, Greek, British, Unknown) indicate:_____

Racial Origin(s) <u>Father</u>:
☐ Caucasian
☐ Jewish ☐ Indian subcontinent
☐ Asian
☐ Chinese ☐ SE Asian
☐ Other (specify) _____
☐ Aboriginal
☐ Mixed (specify):_____
☐ Other (specify): _____
Unknown
Ethnic Origin Father (eg Anglo-Saxon, Italian, Greek, Unknown) indicate:_____

Yes No ?
☐ ☐ ☐ **Family History of IBD in First Degree Relative** (ie mother/father/sibling)
If Yes - specify (eg Father - Crohn's disease): _____
Yes No ?
☐ ☐ ☐ **Smoker** living in House **at Diagnosis**
☐ ☐ ☐ Exposed to Smoker living in House Ever

E. OTHER DIAGNOSES

Coexisting Major Diagnoses or Conditions (other than IBD related) at diagnosis eg Turner's syndrome, Asthma, Leukaemia, Liver transplant etc

_____
_____
_____

F. NUTRITIONAL PROFILE AT DIAGNOSIS

Weight ____.____kg
Height ____.____cm
Pubertal development (Tanner stage 1-5) _____

	Yes	**No**	**?**	
Menarche	☐	☐	☐	If Yes, age in years: _____

G. LABORATORY DATA AT DIAGNOSIS

Hb at diagnosis _____
PCV (haematocrit) _____
Platelets _____
ESR _____
WCC _____
CRP _____
ALBUMIN _____
ALT _____
AST _____
GGT _____
P-ANCA ☐pos ☐ neg ☐ not done

ASCA IgA titre ____ ☐pos ☐neg ☐not done
ASCA IgG titre ____ ☐pos ☐neg ☐not done

Completed by: _____
(print name)

Date _____

Return to: Dr David Moore

Gastroenterology Unit

Children, Youth and Women's Health Service,

North Adelaide

Appendix C

Table 6.12.21: Predictors of change in BMI z-scores in pre/early pubertal children diagnosed with Crohn's disease.

Predictors at Diagnosis	**Estimate**	**95% Confidence interval**	**p-value**	**Sample size**	**Multivariate p-value[a]**	**Multivariate p-value[b]**	**Multivariate p-value[c]**
Within first year (difference between 1st year and diagnosis)							
BMI z-score (entire cohort)	-0.451	-0.63, -0.272	<0.001	44		<0.001	<0.0001
BMI z-score (female)	-0.558	-0.844, -0.273	0.001	19		N/A[p]	N/A[p]
BMI z-score (male)	-0.345	-0.588, -0.103	0.007	25		0.01	N/A[p]
Age at diagnosis (yrs)	0.101	0.017, 0.184	0.018	44	N/A[d]	0.026	0.009
PCDAI score	0.0286	0.012, 0.046	0.001	44	N/A[e]	0.003	0.024
Endoscopic colitis score	0.248	0.047, 0.449	0.016	42	0.119	0.029	0.076
WCC (10^9/L)	0.000	0.000, 0.000	0.005	44	0.095	0.01	0.017
ESR (mm/hr)	0.014	0.003, 0.024	0.014	43	0.376	0.023	0.171
CRP (mg/L)	0.0074	0.001, 0.015	0.047	39	0.331	0.066	0.236
Albumin (g/L)	-0.068	-0.106, -0.029	0.0005	42	N/A[f]	0.002	0.007
Within first 2 years (difference between 2nd year and diagnosis)							
BMI z-score (entire cohort)	-0.372	-0.58, -0.165	0.0009	40		0.001	0.002
BMI z-score (female)	-0.601	-0.912, -0.289	0.0012	16		N/A[p]	N/A[p]
BMI z-score (male)	-0.159	-0.443, 0.124	0.2566	24		0.259	N/A[p]
PCDAI	0.0309	0.0133, 0.0485	0.0006	39	N/A[g]	0.001	0.0084
Endoscopic colitis score	0.2814	0.078, 0.4847	0.0067	38	0.031	0.011	0.0272
Hb (g/L)	-0.0192	-0.0374, -0.001	0.0386	39	0.137	0.061	0.2882
WCC (10^9/L)	0.0000	0.0000, 0.0000	0.0012	39	0.032	0.005	0.0097
ESR (mm/hr)	0.0158	0.0045, 0.0271	0.0062	38	N/A[h]	0.012	0.0808
CRP (mg/L)	0.0092	0.0012, 0.0171	0.0234	34	0.067	0.04	0.1249
Albumin (g/L)	-0.0728	-0.1142, -0.0315	0.0006	37	N/A[i]	0.002	0.0039
Within the first 5 years (difference between 5th year and diagnosis)							
BMI z-score (entire cohort)	-0.407	-0.655, -0.158	0.0027	25		0.002	N/A[p]
BMI z-score (female)	-0661	-0.903, -0.419	0.0004	10		N/A[p]	N/A[p]

BMI z-score (male)	-0.124	-0.484, 0.236	0.4706	15		N/A[p]	N/A[p]
Age at diagnosis (yrs)	0.124	0.008, 0.2405	0.0362	25	N/A[j]	0.031	N/A[p]
Inflammatory (B1) vs stricturing (B2)/penetrating (B3) behaviour	-1.689	-3.043, -0.335	0.017	25	0.02	0.018	N/A[p]
Inflammatory (B1) vs stricturing (B2) behaviour	-1.914	-3.832, 0.004	0.05	24	0.137	0.03	N/A[p]
Inflammatory (B1) vs penetrating (B3) behaviour	-1.464	-3.382, 0.454	0.128	24	0.062	0.233	N/A[p]
PCDAI score	0.0254	0.0039, 0.0468	0.0203	25	N/A[k]	0.024	N/A[p]
Endoscopic colitis score	0.2936	0.0028, 0.5844	0.0478	23	0.136	0.029	N/A[p]
Perianal fistula (present vs absent)	1.352	0.059, 2.6449	0.0404	25	N/A[l]	0.055	N/A[p]
Perianal abscess (present vs absent)	1.352	0.059, 2.6449	0.0404	25	N/A[m]	0.055	N/A[p]
WCC (10^9/L)	0.0000	0.0000, 0.0000	0.0016	25	N/A[n]	0.012	N/A[p]
Albumin (g/L)	-0.0681	-0.1141, -0.0221	0.0037	24	N/A[o]	0.006	N/A[p]

N/A: analysis not possible

[a]Multivariate analysis with the inclusion of diagnostic BMI z-score.

[b]Multivariate analysis with the inclusion of systemic corticosteroid duration during the specified period.

[c]Multivariate analysis with duration of systemic corticosteroids during the specified period and early use of azathioprine as covariates.

[d]Strong correlation between diagnostic age and diagnostic BMI z-score (Pearson correlation: -0.467; 1-tailed p-value: 0.001).

[e]Strong correlation between diagnostic PCDAI and diagnostic BMI z-score (Pearson correlation: -0.444; 1-tailed p-value: 0.001).

[f]Strong correlation between diagnostic albumin value and diagnostic BMI z-score (Pearson correlation: 0.474; 1-tailed p-value: 0.001).

[g]Strong correlation between diagnostic PCDAI and diagnostic BMI z-score (Pearson correlation: -0.471; 1-tailed p-value: 0.001).

[h]Strong correlation between diagnostic ESR and diagnostic BMI z-score (Pearson correlation: -0.407; 1-tailed p-value: 0.006).

[i]Strong correlation between diagnostic CRP and diagnostic BMI z-score (Pearson correlation: 0.51; 1-tailed p-value: 0.001).

[j]Strong correlation between diagnostic age and diagnostic BMI z-score (Pearson correlation: -0.445; 1-tailed p-value: 0.013).

[k]Strong correlation between diagnostic PCDAI and diagnostic BMI z-score (Pearson correlation: -0.433; 1-tailed p-value: 0.015).

[l]Strong correlation between presence of perianal fistula at diagnosis and diagnostic BMI z-score (Pearson correlation: -0.514; 1-tailed p-value: 0.004).

[m]Strong correlation between presence of perianal abscess at diagnosis and diagnostic BMI z-score (Pearson correlation: -0.514; 1-tailed p-value: 0.004).

[n]Strong correlation between diagnostic WCC and diagnostic BMI z-score (Pearson correlation: -0.452; 1-tailed p-value: 0.012).

[o]Strong correlation between diagnostic albumin and diagnostic BMI z-score (Pearson correlation: 0.562; 1-tailed p-value: 0.002).

[p]Small sample size.

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