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The Development of a Decision Aid for Patients with Ulcerative Colitis Deciding Between Ileostomy or Ileal Anal-Pouch Reconstruction

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THE DEVELOPMENT OF A DECISION AID FOR PATIENTS WITH ULCERATIVE COLITIS DECIDING BETWEEN ILEOSTOMY OR ILEAL ANAL-POUCH RECONSTRUCTION

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By

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ABSTRACT

Objectives: To develop a prototype decision aid used to assist ulcerative colitis patients when deciding between ileal pouch-anal anastomosis (IPAA) and ileostomy.

Methods: Three separate systematic reviews (quality of life studies, IPAA studies, ileostomy studies) were conducted to populate the decision aid with outcome probabilities. Meta-regression was used to select appropriate pooled outcomes.

Results: Of 3920 studies reviewed, 9 studies reported on quality of life, 67 on outcomes following IPAA, and 11 following ileostomy. No difference in quality of life was found between procedures. Among IPAA patients, pooled pouch failure rate was 5.5%, with pouchitis being the most common complication (22%). Among ileostomy patients, the pooled rate of ileostomy revision was 17.1%.

Conclusions: No surgical option is clearly superior and patients must weight specific risks and benefits in deciding between procedures. This newly developed decision aid may help patients decide which option is best for them.

KEYWORDS: Ulcerative Colitis; Decision Aid; IPAA; Restorative Pouch; Quality of Life; Ileostomy

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Meaning
AD	Anti-Diarrheal
BM	Bowel Movement
DALM	Dysplasia-Associated Mass or Lesion
FAP	Familial Adenomatous Poplyposis
HRQL	Health-Related Quality of Life
HLA	Human Leukocyte Antigen
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IPAA	Ileal Pouch-Anal Anastomosis
MHC	Major Histocompatibility Complex
NA	Not Applicable
NR	Not Recorded
NS	Not Significant
SBO	Small Bowel Obstruction
SD	Standard Deviation
SF-36	Short-Form 36
SIP	Sickness Impact Profile
TNF	Tumor Necrosis Factor
TTOT	Time Trade-Off Technique
UC	Ulcerative Colitis
VAS	Visual Analogue Scale

CHAPTER ONE-INTRODUCTION

1.0 Overview

Some therapeutic decisions faced by patients are easy for example, use of antibiotics to treat an infection or having surgery to remove a cancer. Few patients would find difficulty deciding between leaving an ultimately fatal cancer to grow or removing it with surgery. Other decisions in medicine are not as clear with the benefit of one treatment option over another depending on the balance of differing complications and outcomes associated with each treatment. One example is the decision between a lumpectomy and radiation after lumpectomy (breast conserving surgery) or a mastectomy faced by women with localized breast cancer. Both treatment options are associated with equivalent survival[1] but the implications of the treatment and its consequences for the patient are different. Women faced with this decision must balance the increased locoregional recurrence rate and need for adjuvant radiation associated with breast conserving surgery versus the more invasive mastectomy entailing the removal of the entire breast but sparing the need for radiation. This is a difficult decision as it comes at an emotionally charged time and requires the assimilation of complex medical information to properly weigh the risks and benefits of each option.

In an effort to enhance and support this decision making process, researchers at McMaster University developed a decision aid to assist patients and their clinicians when discussing these treatment options[2]. Their decision aid consisted of a visual aid and written material systematically developed to present the information based on the best available evidence to the patient during the surgical consultation. This decision aid was subsequently tested in a randomized controlled trial involving women who faced the

decision of breast conserving surgery or mastectomy. Use of the aid was not only associated with improved patient knowledge about the two treatment options, but also improved satisfaction and reduced decisional conflict[3]. Thus, the use of the aid not only enhanced the decision making process but left women more satisfied with their chosen treatment.

A similarly complex decision faces patients with ulcerative colitis. Approximately one third of patients with ulcerative colitis will ultimately undergo a proctocolectomy (removal of the entire colon and rectum) for the management of their disease[4]. Following the removal of the colon and rectum, patients have two main reconstructive options. Both options involve trying to overcome the loss of the reservoir function provided by the rectum which is pivotal to maintaining control of bowel function on a day to day basis. One is to restore intestinal continuity by fashioning a neo-rectum using the ileum and anastomosing (joining) it to the anus, a procedure known as ileal pouch-anal anastomosis (IPAA). This strategy results in a new rectum formed by the small bowel, thus patients continue to have bowel movements via their anuses, but the frequency of movements is increased (6-20 times per day). The other surgical option is to bring the end of the ileum out to the skin as an ileostomy. This procedure results in patients passing feces through the ileostomy and into an appliance. Both of these options result in very different experiences, complications, and implications for day to day life. This is a complex decision with lots of factors to consider for patients, and as no option has been shown to be superior to the other[5], patient preference for either procedure guides the therapeutic decision[6].

1.1 Objective

To our knowledge, no decision aid has been developed to support and facilitate the decision between surgical options faced by patients with ulcerative colitis. The objective of this thesis was to develop a prototype decision aid for patients with ulcerative colitis who are undergoing an elective proctocolectomy and have to choose between IPAA and ileostomy. This work represents the first step in developing a decision aid that will ultimately be refined and evaluated by patients with ulcerative colitis. In order to appreciate the necessity for the aid, background information detailing the role of surgery in the management of ulcerative colitis and the different surgical options will be presented in the first chapter. This introductory chapter will also include information about decision aids and will outline the process of decision aid formation. Subsequent chapters will deal with the literature review and meta-analyses necessary to populate the decision aid with information based on the best available evidence. Finally the prototype decision aid and its plan of refinement will be presented.

1.2 Ulcerative Colitis

Ulcerative colitis is one of two major forms of inflammatory bowel disease (IBD), the other being Crohn's disease, and together they affect approximately 0.5% of Canadians[7]. Although often lumped together, Crohn's disease and ulcerative colitis represent distinct clinico-pathologic entities. Ulcerative colitis is limited to the mucosa of the bowel wall, while Crohn's disease involves transmural inflammation. They differ in their distribution as well, with ulcerative colitis being limited to the rectum and colon, while Crohn's disease can occur anywhere along the gastrointestinal tract[8].

In ulcerative colitis, chronic inflammation of the colon and rectum induces symptoms of diarrhea, abdominal pain, bloody stools, and weight loss. In its most severe form, the disease results in a life-threatening colonic emergency (fulminant colitis) characterized by systemic sepsis and multi-organ failure. In addition to these effects, it also places patients at increased risk of colon cancer. Medical treatment may temporarily control symptoms but the only definitive treatment is surgical removal of the entire colon and rectum. What follows is a brief look at the epidemiology, risk factors, clinical features, diagnosis, and treatment of ulcerative colitis with specific emphasis on the role of surgery and the surgical options.

1.2.1 Epidemiology

Ulcerative colitis is a disorder of the developed world, with the highest annual incidences being found in Europe (24.3/100 000 person-years) and North America (19.2/100 000 person-years) when compared to Asia and the Middle East (6.3/100 000 person-years)[9]. Although first described in the 19th Century, the incidence and prevalence of ulcerative colitis have been increasing[10, 11]. In Canada, the estimated prevalence of ulcerative colitis is 211.2/100 000 with an annual incidence of 12.9/100 000 person-years[7]. With an estimated population of 34 million in 2010, there were approximately 4000 new cases of ulcerative colitis diagnosed in that year alone[12]. Ulcerative colitis is considered to have a bi-modal age distribution with most patients developing the disease in early adulthood and a second peak of incidence in the 50-60 age range[13]. Mean age of diagnosis of inflammatory bowel disease in North America ranges from 33-45 years[14], with ulcerative colitis developing 5-10 years later than Crohn's disease[15]. The gender distribution of ulcerative colitis is fairly even, however, men are more likely to develop

disease later in life[16]. In Canada, the incidence ratio between females and male is roughly 1.05, while Crohn's disease displays a female predilection with a ratio of 1.33[7].

Given its chronic nature and increasing incidence, ulcerative colitis represents a large burden on the Canadian health care system. The direct yearly cost of caring for a patient with ulcerative colitis on the Canadian health care system is estimated at $3500 per patient. This number is much higher for those who require surgery with an estimated yearly cost of $18,749 during the year of surgery[17]. Contributing to this cost is the frequency of hospitalization which is twice that of the normal population, with an average cost of $5000 per hospitalization[12]. Added to this is the indirect cost of lost productivity as patients with ulcerative colitis missed on average 7.2 days of work in 2008, contributing to approximately $150 million dollars in lost productivity due to inflammatory bowel disease[18]. Despite its significant societal and economic impact, the exact cause of ulcerative colitis remains elusive.

The most established theory on the etiology of inflammatory bowel disease is one of an environmental trigger inducing an inflammatory response in a genetically susceptible host[19]. According to this concept a luminal trigger, whether it be an infectious agent (bacteria/parasite/virus) or some environmental or nutritional antigen, induces a dysregulated, chronic, inflammatory response within the colon and rectum[20]. The evidence for this theory comes largely from epidemiologic and clinic-pathologic studies of risk factors and genetic associations.

1.2.2 Risk Factors

Congruent with the environmental trigger-susceptible host theory of pathogenesis, risk factors for ulcerative colitis and inflammatory bowel disease can be divided into *genetic* factors and *environmental* factors.

Genetic Factors

Evidence of a genetic predilection for inflammatory bowel disease comes from studies showing clustering of cases within families. Family members of patients with ulcerative colitis have a 10 fold increase in contracting the disease when compared to age and sex matched controls[21]. Further evidence is garnered from twin studies where the monozygotic concordance rates are 18% for ulcerative colitis and 58% for Crohn's disease[22]. Families with multiply affected kindred also show a pattern of disease type with 75% of those affected having one type of IBD only[23]. Although not consistent with classical patterns of genetic inheritance (autosomal dominant, x-linked, etc) these associations suggest a myriad of genes interplaying to produce a variable level of susceptibility to IBD.

Currently, over 60 distinct genetic susceptibility loci have been linked with IBD[24]. The most established genetic link has been made with genes encoding for the major histocompatibility complex (MHC) on chromosome 6, known as the *HLA* genes[25, 26]. MHC is a protein complex found on the cell membranes of all cells in the body. They mediate the interaction between white blood cells and other cells, and are implicated in immune function and autoimmune diseases. The most consistent association with ulcerative colitis has been the *DRB1*0103* allele. Found in less than 2% of the Caucasian population, studies have identified the allele in up to 15.8% of patients with extensive

colitis requiring surgery, suggesting it may also be associated with disease severity[26, 27].

Other genes associated with ulcerative colitis include cellular signalling pathway genes

(*JAK2, STAT3*)[28] and intestinal barrier function genes (*ECM1,HNF4A*)[29, 30]. The latter

group of genes encode for cell-adhesion molecules that help maintain the integrity of the

intestinal mucosa. Their association with ulcerative colitis supports the long-held belief

that compromised, "leaky", mucosa is part of the pathogenesis of the disease[31]. It is

genetic attributes such as these that make a patient susceptible to the development of the

disease which is thought to result from exposure to some form of environmental trigger.

Environmental Factors

One of the strongest links to the importance of environmental factors in the

pathogenesis of ulcerative colitis comes from the consistent finding of an increasing

incidence of IBD in Western developed countries when compared to developing

countries[32]. When immigrants from a low incidence, developing country, travel to a

Westernized country, it is their children that develop an increased susceptibility to

inflammatory bowel disease suggesting childhood exposure to the environmental triggers

is key. It is these associations which have lead some credence to the so-called hygiene

hypothesis or "dirty" hypothesis of autoimmune diseases. According to this theory,

children that have limited exposure to bacteria from living in "sterile" modern

environments have abnormally developed immune function and are unable to

differentiate between pathogenic and non-pathogenic antigens. This results in non-

pathogenic antigens, whether their own or from commensal bacteria (gut flora), inducing

chronic inflammatory reactions leading to autoimmune diseases such as IBD[33]. The

dysregulation of the immune system is thought to arise from dysfunction of regulator T-

cells resulting from limited exposure to both commensal and pathogenic bacteria during childhood and infancy[34]. Many features of life in a modern society are linked to reduced bacterial exposure: improved sanitation, decline in endemic parasitism, life on concrete with reduced exposure to soil, increase in antibiotic use, vaccination, and less crowded living conditions[32]. Despite ample evidence for the hygiene hypothesis, the specific environmental trigger(s) for IBD remain elusive. Many dietary or infectious agents have been proposed but none have been conclusively linked[16].

The specific trigger(s) and pathogenesis of IBD remain unclear, although most of the evidence supports the environmental trigger-susceptible host theory and the hygiene hypothesis as potential mechanisms. Given its purported autoimmune nature, many of the therapeutic measures have been aimed at altering the immune response within the colon and rectum.

1.2.3 Clinical Features and Diagnosis

Ulcerative colitis is characterized by inflammation affecting the mucosa and submucosa of the rectum and colon. It progresses from the rectum proximally along the colon, with the extent and severity of inflammation dictating the symptomatology of the patient. The most common findings are bloody diarrhea, urgency, and tenesmus. As the disease progresses proximally patients may complain of abdominal pain and fever. Most patients have disease limited to the left colon and rectum (80%), while 20% will develop inflammation throughout the colon[40]. Patients may also develop extra-intestinal inflammatory manifestations involving the skin (pyoderma gangrenosum, erythema nodosum), eye (uveitis, scleritis), joints (ankylosing spondylitis, sacroilitis), and

hepatobiliary system (sclerosing cholangitis). These manifestations occur in approximately 30% of patients, with the joint complications being most common[41]. Some ocular and skin disorders will improve following colectomy while hepatic and articular disorders do not, with some patients requiring a liver transplant for sclerosing cholangitis[42].

The disease course and severity is variable with some patients experiencing a waxing and waning course with occasional disease flares and periods of remission, while others experience severe un-remitting disease. Diagnosis is usually accomplished via endoscopy of the rectum and colon demonstrating mucosal inflammatory changes (redness, exudates, ulceration, loss of mucosal folds), and biopsies of the rectal/colonic wall displaying signs of chronic inflammation (cryptitis and crypt abscesses) and architectural distortion (crypt branching, loss of goblet cells)[43]. Other diagnostic considerations include Crohn's disease, infectious colitis, radiation colitis, and ischemic colitis. In its most severe form, ulcerative colitis can present as fulminant toxic colitis with associated systemic sepsis and evolving organ failure. Other urgent complications include gastrointestinal haemorrhage, perforation, and severe dilatation of the colon (megacolon).

One chronic consequence of long-term inflammation in the colon and rectal mucosa is a predilection for the development of colorectal adenocarcinoma. This risk is first materialized at approximately the 8-10 year mark following disease onset with an associated risk of colon cancer of approximately 2%[44]. This risk increases with length of disease activity to roughly 20% at 30 years[45]. The development of cancer is preceded by pre-cancerous changes in the mucosa (low and high grade dysplasia), the detection of

which usually mandates the removal of the entire colon and rectum as up to 40% of patients with dysplasia will harbour a malignancy. This forms the rationale behind colonoscopic screening guidelines which recommend that patients with ulcerative colitis have a colonoscopy every 1-2 yrs with random biopsies to assess their risk of having colon cancer starting at 8-10 years of disease activity[46, 47].

1.2.4 Treatment Overview

Most cases of ulcerative colitis can be treated medically with anti-inflammatory medications. Medical therapy is aimed at either the control of acute symptoms with induction of remission or the maintenance of disease remission. The specific agents chosen depend on the severity and location of disease. Mild disease limited to the recto-sigmoid area (distal colon and rectum) is usually treated with topical therapies, either 5-ASA compounds or steroid enemas. More severe proximal disease may require systemic therapy, again with either 5-ASA compounds or steroids. Mild diffuse colonic disease usually necessitates systemic therapy with 5-ASA compounds, while severe acute disease is often treated with steroids[48]. Most cases will respond to steroids, but a small subset will require emergency surgery for severe steroid-refractory disease. Once a patient recovers on steroids, they are slowly weaned off and disease activity is monitored. Because of severe side effects, long-term steroid therapy is not recommended to maintain remission, thus other immunomodulators are used to treat steroid-dependent disease, where symptoms persist or recur following steroid taper. Compounds such as 6-mercaptopurine and azathioprine are used to blunt the body's immune system and allow the tapering of steroids. Other newer biologic medications, antibodies designed to target specific molecules in the inflammatory cascade, are also used to treat steroid refractory disease.

Infliximab, a monoclonal antibody active against tumor necrosis factor alpha (TNF), is used to treat steroid dependent or resistant disease, to both induce and maintain remission[49]. Most patients can be successfully managed with medical treatment alone but up to 25% will ultimately require surgery for the treatment of their disease[4, 50].

1.2.5 Role of Surgery

One of the major differences between Crohn's disease and ulcerative colitis is the ability to cure ulcerative colitis with removal of the rectum and colon (proctocolectomy). The indications for surgery can be grouped by urgency with both elective and emergent conditions requiring surgery. The most common elective indication for surgery is failure of medical management[4, 51]. These are patients who have ongoing symptoms despite medical management, or who are unable to tolerate the withdrawal of steroids. The use of newer agents, such as infliximab, has not reduced the need for colectomy[52]. Another elective indication for surgery is increased risk of cancer. Total proctocolectomy is recommended for patients with ulcerative colitis who have a current colon cancer, dysplasia associated lesion or mass (DALM), or high grade dysplasia. Both DALM and high-grade dysplasia are associated with high risks of concurrent adenocarcinoma with up to 40% rates of concurrent cancer identified when the specimens are reviewed pathologically[53]. The recommendations are less clear for patients with low grade dysplasia, as the risk of concurrent cancer is less well defined with risks of developing future high grade dysplasia or cancer ranging from 18-54%[54-56]. Most practitioners would recommend surgery in a good risk patient but obviously the decision is highly individualized based on patient factors[51, 57].

Severe acute colitis affects 10-15% of patients with ulcerative colitis and is characterized by frequent bloody bowel movements, fever, tachycardia and anemia. Such patients may progress to develop fulmitant colitis characterized by systemic sepsis and evolving organ failure, or develop megacolon defined as transverse colonic dilatation greater than 6 cm. Both of which are generally considered indications for emergent surgery[4, 51]. Approximately 20-30% of patients with severe acute colitis will require surgery[58]. The surgical options considered in the emergent setting differ from the elective situation. The sole priority during emergent surgery is to remove the source of systemic toxicity, the colon, thus subtotal colectomy with ileostomy is the procedure of choice[51, 59]. This entails leaving the rectum in-situ as removal of the rectum entails a more involved procedure with increased risks of morbidity and potentially mortality, and disease of the rectum alone is rarely life-threatening. Reconstructive options such as an ileal pouch-anal anastomosis are not appropriate in the acute setting given the increased complexity of the surgery. Removal of the rectum with IPAA can be considered electively months later once the patient has recovered from their acute illness. Patients who develop colonic perforation are also treated with a subtotal colectomy and ileostomy, although they carry a much higher mortality[60, 61]. Patients with acute colitis who fail to respond to medical management within 72-96 hours should also be offered colectomy[62]. Following a subtotal colectomy and ileostomy, these patients have the option to choose from either keeping their ileostomy or undergoing a restorative pouch procedure. Electively, patients have options to choose from, these will be described in the following section.

1.2.6 Elective Surgical Options

Patients who have elective surgery for ulcerative colitis, whether it is for intractability or cancer risk, have options to choose from. The main options are either a total proctocolectomy (removal of entire colon and rectum) and ileostomy, or total proctocolectomy with ileal pouch-anal anastomosis (IPAA). Other options such as the continent ileostomy (Koch pouch) and ileoproctostomy have very limited roles in the modern surgical management of ulcerative colitis and have largely fallen out of favour. The Koch pouch has been associated with a high rate of revision and re-operation (up to 50%), while the ileoproctostomy leaves the rectum insitu which is at risk of malignancy[4].

Total proctocolectomy and ileostomy

This procedure involves the removal of the entire colon and rectum, and the connection of the end of the small bowel to the skin (ileostomy or stoma). Digested material passes through the small bowel and is emptied into a bag that is worn on the skin with the aid of an appliance. It is the conventional, benchmark procedure for ulcerative colitis to which all others are compared. It is well established as being safe and allows patients to continuing living active lives[63]. It is considered the first line procedure in those who choose to undergo it rather than IPAA, or those who are not candidates for IPAA (impaired fecal continence, peri-anal disease, multiple comorbidites)[51]. It has the benefit of only requiring one procedure whereas restorative proctocolectomy (IPAA) is often done as a staged procedure. Complications following this procedure include stoma related complications (prolapse, retraction, peri-stomal hernia), small bowel obstruction, unhealed perineal wound, and sexual and bladder dysfunction[64-67]. The most distressing feature of this procedure for patients is the creation of the ileostomy. This necessitates

emptying the bag of small bowel feces roughly 6-10 times per day. Although the idea of a stoma seems difficult to accept for patients, most patients who undergo the procedure are satisfied with their result[6, 68, 69]. A systematic review of outcomes following this procedure will be presented later in the thesis, while a separate chapter will be devoted to a quality of life comparison between this procedure and IPAA.

Ileal pouch-anal anastomosis (IPAA)

During this procedure, the small bowel (ileum) is used to construct a pouch that functions as a neo-rectum allowing patients to defecate via their anus. The only true advantage it has over the traditional therapy is the avoidance of an ileostomy and the restoration of anatomic defecation. This advantage does come at a cost of a more lengthy procedure with its own set of complications and risks. Most of these complications are related to the creation and malfunction of the ileal pouch, which does not function perfectly as a new rectum. In this option patients typically have a staged surgery where the colon and rectum are removed, the pouch created and the fecal stream diverted proximal to the pouch with a loop ileostomy. This ileosotmy is later closed during a second procedure. Chapter three will summarize a detailed systematic review of trials comparing the quality of life between ileostomy and IPAA, while Chapter four will review the outcomes following IPAA.

1.3 Decision Aids

Most clinical decisions faced by patients and surgeons involve the balance of risks and benefits. The uncertainty of potentially poor outcomes at the patient level makes this process difficult and distressing to patients and surgeons alike. Traditional models of clinical decision making, namely paternalistic ones where surgeons simply determined

what they felt was the best option for the patient and proceeded with such have been abandoned in favour of a shared-decision making process[77]. At the conceptual level, shared-decision making has four necessary characteristics: 1) Both the physician and the patient are involved in the treatment decision making process. 2) Both the physician and the patient share information with each other. 3) Both the physician and the patient take steps to participate in the decision making process by expressing treatment preferences. 4) A treatment decision is made and both the physician and patient agree on the treatment to implement[78]. Within this framework are three well-defined stages: information exchange, deliberation, and deciding on a treatment. The utility of decision aids are built into this framework by facilitating the information exchange between the patient and the surgeon; and by clarifying a patient's preferences during the deliberative stage of decision making[77].

But do patients want to be involved in their treatment decisions? Two studies have addressed this issue in patients with IBD. In a survey of over 1000 patients with either Crohn's disease or ulcerative colitis, 81% of patients indicated they wanted to be actively involved in their treatment decisions[79]. In a second study of over 1000 patients with IBD, 80% of patients indicated they wanted more information about treatment options when discussing treatments with their physicians[80]. With an obvious desire for more involvement, and with IBD patients being often young and knowledgeable about their condition, this is a population ideally suited for the use of decision aids.

1.3.1 Objectives of a Decision Aid

The main goal of decision aids is to facilitate informed, preference-sensitive decision making[81]. Not all clinical decisions are necessarily "preference-sensitive" and thus some clinical decisions are better suited to the use of decision aids. Wennberg has divided clinical decisions into those that are "effective", meaning decisions where the benefit is clear to both the patient and the physician (antibiotics for an infection) and those that are "preference-sensitive", where the optimal strategy is unclear and depends on the preferences and values of an individual patient[82]. The decision between a restorative pouch procedure or an ileostomy is clearly a "preference-sensitive" decision. Both options result in a similar control of disease, but one avoids the need for an ileostomy at a cost of different complication profile and the need for more procedures. The process of shared-decision making should respect a patient's individual values, personal resources, and capacity for self determination[83]. It is built upon a therapeutic alliance where responsibility for the decision and outcome are shared by the care team[84]. Patients can often find complex medical decision making troubling, a phenomena known as decisional conflict[85]. Uncertainty around the decision and its potential outcomes results not only from the inherent complexity of balancing various risks and benefits, but also from modifiable factors such as lack of information, lack of understanding, unclear values, and inadequate support during the decision making process. O'Connor has developed nine objectives that have been adopted as pillars for the development and design of decision aids: 1) Improve knowledge of the clinical problem, options, outcomes, and variation in patient or practitioner opinions and practices. 2) Create realistic expectations of outcomes, consistent with available evidence. 3) Clarify personal

values for outcomes and promote congruency between patient values and choices. 4) Reduce patients' and practitioners' decisional conflict (uncertainty) about the course of action to take. 5) Promote implementation of choices. 6) Improve patients' and practitioners' satisfaction with decision making. 7) Promote patients' persistence with choice. 8) Reduce patients' distress from the consequences of decisions. 9) Improve patients' health-related quality of life and promote informed use of resources by patients and practitioners[86]. It is along these objectives that decision aids should be designed and evaluated.

1.3.2 Design of a Decision Aid

To develop a decision aid, the first step is the consolidation of the best evidence for the individual treatment options explored. In order to gather the necessary data, a systematic review of outcomes following both IPAA and ileostomy will be undertaken in order to populate the prototype decision aid with data. This will form the rough prototype that will be further refined by input through surgeons, ostomy wound care specialists, and patients themselves. A Delphi conference of experts in the field of decisional support, the International Patient Decision Aid Standards Collaboration, established 12 quality criteria for the development of decision aids which were used as a guide to the development of our aid: 1) systematic development process; 2) providing information about options; 3) presenting probabilities; 4) clarifying and expressing values; 5) using patient stories; 6) guiding or coaching in deliberation and communication; 7) disclosing conflict of interest; 8) delivering patient decision aids on the internet; 9) balancing the presentation of choices; 10) using plain language; 11) basing information on up to date scientific evidence; and 12) establishing effectiveness. The only criterion that we do not consider

significant is the use of patient stories. Some literature has shown the inclusion of patient stories can bias patients' preferences and potentially unduly influencing their decision[87]. Thus patient stories were not included in the development of the aid.

Following the collection of outcome probabilities from the literature, the prototype aid will further be refined by three sets of focus groups, one with colorectal surgeons, one with enterostomal therapists, and one with patients. The resulting refined prototype will then be tested for validity and reliability on healthy volunteers, as it is clinically inappropriate and potentially unethical to manipulate information concerning therapy and outcomes to patients at the decision point[88, 89]. Finally with a valid and reliable decision aid, it will be tested on patients for effectiveness. Various outcomes have been proposed for the evaluation of decision aids. Demonstrating an increase in knowledge about the treatment options by the use of a decision aid is an obvious first step in evaluating the effectiveness of the aid, and is fairly straightforward with the use of pre and post questionnaires. Moving beyond a demonstration of improved knowledge acquisition, the purpose of the decision aid is to enhance the overall decision making process and ultimately result in an improved quality of life for the patient. Various scales have been developed to test the conceptual aspects of an enhanced decision making process. One of the most studies is the Decisional Conflict Scale, developed by O'Connor. This scale operationalizes the degree of uncertainty patients experience when facing a treatment decision. This scale consists of 16 questions with Likert scale responses that explore three domains: decisional uncertainty, factors contributing to uncertainty, and perceived effective decision making. This scale has been validated[85] and used in the evaluation of different decision aids[3]. Other metrics that have been used to

evaluate decision aids include measures of anxiety, satisfaction with the decision[2], and preference for independent decision making[90]. Ultimately the goal of the decision aid is to improve a patient's quality of life. This has been difficult to demonstrate reliably as current generic and even disease-specific measures of health-related quality of life may not be sensitive enough to capture the specific aspects of decisional uncertainty. Thus most of the literature has typically utilized a mixture of patient knowledge, decisional conflict, and satisfaction assessments in combination with the degree of patient participation as ways to establish the effectiveness of these aids. In a systematic review of over 30 trials examining the effectiveness of decision aids, the use of these aids was found to improve patients knowledge, improve the proportion of patients with realistic perceptions of the risks and benefits of the therapies, lower decisional conflict, reduce the proportion of patients who are passive decision makers, reduce the proportion of patients who remain undecided after counselling, and improve the agreement between a patient's values and the option chosen[91]. It is along these metrics that our aid will ultimately be evaluated by.

1.4 Overview of the Thesis

This thesis is designed in the integrated article style, following the introductory chapter, chapter two will describe the methodology behind the systematic literature review and quality assessment necessary for the creation of the prototype decision aid. Chapter three will present the results of the systematic review of quality of life literature comparing ileostomy and IPAA treatment options. Chapter four will summarizes the results of the systematic review and meta-analysis of outcomes following the IPAA option, while chapter five will discuss the results of the outcomes following the ileostomy

option. Finally, chapter six will outline the methodology behind the refinement and

validation of the prototype decision aid.

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CHAPTER TWO **-** SEARCH STRATEGY AND STUDY INCLUSION FOR
SUBSEQUENT SYSTEMATIC REVIEWS

2.0 Introduction

In order to populate our decision aid with information, a systematic review was
undertaken of the literature reporting on surgical outcomes following proctocolectomy
with either an ileal pouch-anal anastomosis (IPAA) or an ileostomy. Concurrent with this
systematic review, studies reporting on the differences in quality of life between the two
approaches were also reviewed. Rather than conduct three different searches of the same
literature, we combined the three searches into one broad literature search. This allowed
the inclusion of a large number of studies in our index search, and eliminated the
redundancy of having to undertake three separate searches of the same databases for
studies reporting on outcomes following proctocolectomy. The implications of this broad
approach resulted in a very large number of abstracts reviewed, allowing the abstract
reviewers the ability to apply *apriori* study inclusion criteria over a wide range of
screened articles. This chapter serves as part of the methods for the subsequent three
chapters which report on the specific results of the systematic reviews of three groups of
articles: studies comparing quality of life between IPAA and ileostomy, studies reporting
on outcomes following IPAA, and studies reporting on outcomes following ileostomy.

2.1 Search Strategy

Studies were identified by searching the following databases in conjunction with
the help of a professional librarian experienced in systematic reviews (Erin Boyce):

- Medline (1978-2009)

- Embase (1978-2009)
- CINAHL
- Cochrane Database of Systematic Reviews

The search strategy used was a combination of MESH (medical subject heading) terms and key words. For example, when searching Medline, the following strategy was used:

MESH terms

Disease identifiers:

ulcerative colitis, inflammatory bowel disease,

Procedure identifiers:

restorative proctocolectomy, ileostomy,

Key words:

Disease identifiers:

Inflammatory bowel disease, ulcerative colitis, IBD, colitis

Procedure identifiers:

Proctocolectom$, colectom$, ileal pouch-anal anastomosis, IPAA, ostom$,

The disease identifiers were combined with the procedure identifiers and the "explode" function was used to further broaden our search. No limits were placed on language at this stage of our search. A similar strategy was employed when searching the other databases mentioned above with modifications taking into account the differences in MESH terms and key words inherent to each specific database. The search was limited to papers published in 1978 or later as this was the year when Parks published the first report on IPAA[1]. The search was last updated on January 30, 2009. In addition to these electronic searches, the references of included studies were hand searched for any

additional studies that met our inclusion criteria. A broad search strategy with no limits

on type of outcome was selected in order to minimize the risk of missing studies that had

been improperly indexed. The specific search strings are included as Appendix A.

2.2 Study Inclusion Criteria

The study inclusion criteria were formulated along a framework encompassing the

population of interest, the intervention of interest, and outcomes of interest. For a study to

be eligible for inclusion in the review, it had to meet all three criteria. Table 2.1 lists the

specific inclusion criteria.

Table 2.1 Inclusion Criteria for Studies

Population	▪ Patients with ulcerative colitis ≥ 18 yrs of age
Intervention	▪ Proctocolectomy with ileostomy ▪ OR ▪ Restorative pouch procedure (regardless of type of pouch) with or without protocolectomy
Outcomes	▪ ONE OR MORE OF ▪ Post-operative mortality ▪ Post-operative complications ▪ *Early*: wound infection, intra-abdominal sepsis, anastomotic dehiscence, perianal sepsis ▪ *Late*: pouchitis, anastomotic stricture, parastomal hernia, pouch failure, bowel obstruction ▪ Re-intervention/ re-operation (excision of pouch, revision of ileostomy) ▪ Bowel function (fecal incontinence, number of bowel movements/day, need for pad, number of appliance changes per day, need for incontinence pads, need for anti-diarrheal medication) ▪ Sexual dysfunction ▪ *Female:* dyspareunia, reduced fertility

	▪ *Male:* impotence, retrograde ejaculation ▪ Quality of life
Methodologic	▪ Study with more than 100 patients OR comparing quality of life between pouch and end-ileostomy ▪ Year of publication $\geq$ 1978 ▪ No previous publication with the same patients from same institution ▪ Report on baseline characteristics of the patients undergoing procedure ▪ English only language

In addition to the content specific inclusion criteria listed above, specific

methodologic criteria were applied to refine the inclusion of studies. The specific

inclusion criteria relating to population, intervention, and outcome need not be justified

given their self-evident nature, but methodologic criteria require some justification. For

the studies looking at clinical outcomes following either the IPAA procedure or

ileostomy, inclusion was limited to studies that reported on 100 patients or more. Larger

studies are more likely to provide a stable estimate of outcomes (complications), but

limiting the inclusion to studies with even higher numbers (> 1000) would likely result in

the inclusion of only a few studies from high volume centers which could bias the results,

as not all patients who would ultimately be using the decision aid would have access to

high volume centers. Outcomes following IPAA have been linked to surgeon and

institution volume, with lower volume centers having poorer results[2]. Thus limiting the

inclusion to studies with 100 patients or more strikes a balance between the desire to

include as many studies as possible, but also to include those with the most stable

estimates of outcome probabilities. Far fewer studies comparing quality of life between

the two procedures have been published and no study size limitation was placed on the inclusion of these studies.

Inclusion was also limited to studies that reported on baseline characteristics (age, sex, underlying diagnosis) as it was necessary to assess these factors in order to assess whether or not the patients undergoing the procedure met the other inclusion criteria (population, intervention). Publications from the same institution reporting on the same cohort of patients were also excluded. In cases where there were multiple publications from the same institution, the most recent publication with the highest number of patients was included, unless different outcomes were reported. This review was also limited to publications reported in English. Given the large number of studies published on this topic, we felt the added benefit of translating articles would not improve the conclusions of the systematic review. Also there is evidence to suggest that the exclusion of non-English language publications does not influence the ultimate conclusions of meta-analyses[3], and that non-English language publications are often of poorer quality[4].

No limitations were placed on study design (retrospective vs prospective), rather this was included in the quality assessment of the studies. The use of broad inclusion criteria with few limitations on study design has been recommended as the preferred strategy when carrying out a meta-analyses of observational studies[5].

All abstracts generated by the search strategies were reviewed independently by two reviewers. Each reviewer indicated whether or not the study met the inclusion criteria and agreement was measured using the *kappa* statistic. Any disagreements were resolved by consensus, and if consensus was not met then a third reviewer was asked to decide. Measurement of reviewer agreement has been recommended by the PRISMA statement

as a way of enhancing the transparency and reliability of the methods used to screen and select studies for inclusion into systematic reviews[6].

2.3 Study Quality Assessment

Assessing the quality of included studies is an essential part of a systematic review[5, 6]. There are two basic approaches to the assessment of study quality or "risk of bias", namely the use of scales or rating scores that reduce the assessment of a study's quality into a score, or the examination of key components of a study's design and relating individual elements of study design with quality. The attractiveness of the scale or score approach lies in its ease of reporting, by attributing a number or rating to each individual study. This rating can then be used as a weight in adjusting any subsequent meta-analysis. Although attractive from a practical perspective, the use of scales and scores has been criticized as over-simplifying the assessment of quality and potentially introducing bias into the results when used as weights in analysis[7, 8]. Most scores are constructed in an "ad hoc" fashion and lack validity, with various study elements being combined that may or may not have an effect on study validity[5, 9]. An approach where individual elements of study design are assessed and evaluated rather than summarized into a score is the preferred method of study quality assessment[5-7].

The assessment of study quality is not as well established for observational studies as it is for randomized controlled trials[5, 10]. Within controlled-trials, specific elements of study design including: concealment of allocation; blinding of outcome assessors, participants, and patients; and proportion of patients lost to follow-up have all been empirically linked to validity of results[11-13]. Although many tools for assessing study

quality of observational studies exists, with one systematic review identifying 86 such tools[10], no one tool can be recommended over others given the lack of empirical evidence relating specific design elements to study validity[10, 14]. As no consensus exists on the specific method of quality assessment for observational studies, individual elements of the included studies were evaluated for their impact on study quality.

Two systematic reviews on the topic of quality assessment in observational studies came to similar conclusions about which items should be included in the quality assessment of observational studies: methods of selecting patients, methods of measuring outcome variables, adjustment for confounding, and completeness of follow-up[10, 14]. These elements formed the basis of our assessment of study quality (Table 2.2). As most of the studies ultimately included in the systematic review of outcomes following either the IPAA or the ileostomy procedures were single center reports of case series with no comparator, it was important to determine whether a significant selection bias was occurring, namely that authors were only including their "best" cases as opposed to including all patients that underwent a procedure when reporting their rates of complications. To identify potential for selection bias, studies were classified as consisting of consecutive patients or non-consecutive patients depending on the method of patient recruitment. Studies were also classified as either prospective or retrospective depending on the timing of patient recruitment relative to when the outcome occurred. Studies that included consecutive patients recruited prospectively were considered to be at less risk of selection bias compared with non-consecutive or retrospective studies. Studies that did include a comparator group (quality of life studies comparing IPAA and ileostomy) were evaluated as to whether or not the authors adjusted for confounding

either in the design or the analysis of the study. Studies that adjusted for confounding

were considered to be at less risk of bias. Given the large number of outcomes of interest

to the systematic reviews (most complications following IPAA or ileostomy) it was

impractical to evaluate specific definitions for specific outcomes. Rather, studies were

classified based on whether the outcomes listed were clearly defined. Studies that applied

specific definitions when assessing outcomes were considered to be at less risk of bias, as

specific definition of outcomes allows the application of systematic outcome assessment,

and limits subjective interpretation by the individual outcome assessor. Although blinded

outcome assessment has been linked to study validity[12, 13], this measure was not

applicable to most studies in our review given the predominance of single group case

series.

For the group of studies reporting on quality of life comparisons between IPAA and

ileostomy, whether or not the study utilized a validated quality of life measure was

recorded. Studies that utilized a validated measure of quality of life and made reference to

the method of validation were considered to be of less risk of bias when compared to

studies that utilized non-validated measures of quality of life[15].

Loss to follow-up was also considered a quality measure, as controlled-trial literature

has shown it to be associated with study validity. Length of follow-up was also included,

as many of the important outcomes following either procedure can be time dependent.

For example, 45% of patients who will ultimately develop pouchitis, an important

complication following IPAA, will only do so at least 6 months following the

procedure[16]. Along with completeness and length of follow-up, we considered studies

that had a standardized protocol for follow-up, meaning routine clinical assessments at

pre-specified time points, to be more likely to accurately detect and report complications

following either procedure and thus be at less risk of bias.

Table 2.2 Study Elements Evaluated for Quality

Quality Criteria	Categories
Selection	**Non-consecutive**: if patients were recruited from a specific clinic/ institution but no mention is made if they are consecutive or represent all patients from that clinic over a specified time period **Consecutive:** if patients were recruited in a consecutive manner OR represent all patients who presented to a specified clinic/institution over a specified time period **Retrospective**: If the study reports on patients whose outcomes occurred before the study began **Prospective**: If the study reports on patients whose outcomes occurred after the study began
Confounding	**Adjustment**: if the authors adjusted either in the design (matching) or analysis (multivariable methods, stratification) of their study for the presence of confounders. **No adjustment** **No comparator group**: if the study did not include a comparator group
Outcome criteria clearly defined	**All:** if the authors defined their criteria for all the outcomes reported in the study **Some**: if the authors only defined some of the outcomes reported in the study **None:** if none of the reported outcomes were defined
Quality of life instrument	**Validated**: If study reports on the validation method or referenced a study which details the validation method used **Not Validated**: No mention of validation of the instrument/ measure
Loss to follow-up	% of patients not accounted for in the results

Length of follow-up	• mean or median length of follow-up reported in months
Follow-up protocol	• **Standardized:** Standardized follow-up protocol with routine visits at pre-specified time points • **Non-standardized:** Follow-up was not completed in a standardized fashion or no mention of follow-up procedures

Each element of study quality was reported for the individual studies and their influence on the results was explored using sensitivity analyses.

2.4 Results of Study Search

The search strategy outlined previously was last updated on January 30, 2009. In addition to these electronic searches, the references of included studies were hand searched for any additional studies that met our inclusion criteria. Figure 2.1 summarizes the results of the searches. Once duplicates were removed, 3920 distinct abstracts were independently reviewed by two reviewers and any study that either party felt met inclusion criteria was selected for full text review[1]. Of the 3920 abstracts, 411 were ultimately selected for full text review. Of these 411 abstracts, the majority were excluded from final study inclusion. The most common reason for exclusion was a publication dealing with the same cohort of patients published at different time points. In cases were multiple publications dealt with the same cohort of patients, the study with the inclusion of the larger number of patients was used in the review. Studies meeting inclusion were divided into three groups that form the basis of the three meta-analyses to follow. Chapter three of this work will deal with the results of the literature review surrounding quality of life comparisons between IPAA and ileosotmy, while chapters

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[1]A file containing the list of abstracts reviewed is available from the author as it was too large to included as an appendix.

four and five will summarize the results of the meta-analyses of studies reporting on outcomes following IPAA, and ileostomy respectively. The first review is necessary as part of the justification process for a decision aid, if one strategy is clearly superior to the other in terms of quality of life then it throws the very idea of a decision aid into question, and at the very least, any important difference in quality of life must be included in the aid. The other two meta-analyses are necessary to populate the decision aid with outcome probabilities.
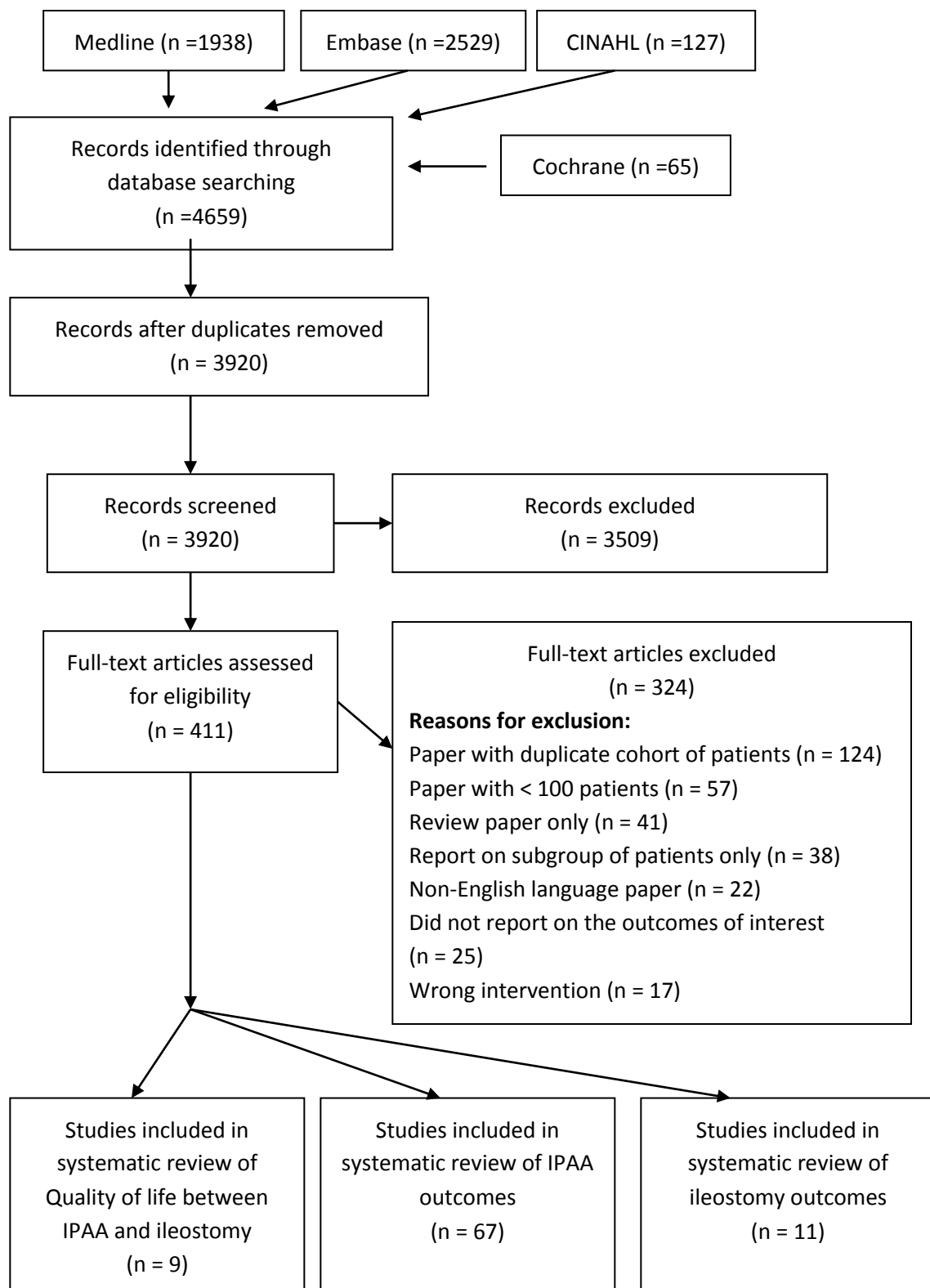
Figure 2.1 PRISMA[6] Flow Diagram of Identified Studies

2.5 References

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CHAPTER THREE-A SYSTEMATIC REVIEW OF STUDIES COMPARING
QUALITY OF LIFE BETWEEN IPAA AND ILEOSTOMY

3.0 Introduction

Whether ulcerative colitis is treated with a proctocolectomy and ileostomy or with an ileal pouch-anal anastomosis (IPAA), the resulting control of disease, namely the removal of the diseased colon and rectum is the same. What differs is the post-operative experience of the patient and the impact each option has on the patient's day to day life. In patients with inflammatory bowel disease who have not had surgery, fears and worries surrounding surgery and the potential need for an ostomy appliance are most prominent when compared to other concerns[1]. Patients with active, symptomatic ulcerative colitis generally have worse health-related quality of life (HRQOL) than healthy controls[2-4]. Severity of disease activity is one of the most important determinants of health-related quality of life in patients with ulcerative colitis[2, 5-7]. Removing the colon and rectum in patients with ulcerative colitis is often curative, and several studies have documented similar HRQOL between patients following colectomy and the general population[8-11]. Studies examining changes in HRQOL between preoperative and postoperative patients have similarly shown an improvement following colectomy[12, 13]. Muir et al in a prospective study of patients undergoing IPAA showed an improvement in both disease-specific and generic measures of health-related quality of life when pre and post-operative scores were compared[12]. These findings have not been universal as Berndtsson and Oresland showed no difference in generic HRQOL between preoperative and postoperative patients undergoing IPAA, and only a modest gain in disease-specific HRQOL[14]. With intractability of disease as the most common indication for proctocolectomy, most patients can expect to have improved HRQOL following surgery.

The question becomes: Does the form of intestinal reconstruction, IPAA or ileostomy, influence the HRQOL of these patients or is the gain in HRQOL independent of which procedure patients receive?

In order to justify the design and application of a decision aid to help patients select which reconstructive option they would prefer, it is necessary to explore the specific effects each has on HRQOL. If one option is clearly superior in regards to HRQOL, then perhaps the role of a decision aid becomes less important as one option may be recommended over the other on the basis of improved HRQOL. If, on the other hand, they are shown to be largely equivalent then helping patients make the choice that is most in keeping with their values and expectations is of paramount importance and the role of a decision aid becomes vital in facilitating such a process. What follows is a systematic review of studies comparing proctocolectomy with IPAA or ileostomy and their effects on HRQOL. Before describing the methodology and results, a brief introduction to the concept of health-related quality of life is necessary to provide context for the remainder of the chapter.

3.1 Health-Related Quality of Life

Health-related quality of life seeks to measure the functional impact a disease and its therapy have on a patient's day to day life[15]. It moves beyond measuring the specific disease state (symptoms, complications) by encompassing behaviours, emotional attitudes, and perspectives of an individual and how they related to their current state of health[16]. Measuring HRQOL is important as two patients may have identical disease severity yet one will have a job and a healthy social life, while the other is unemployed,

depressed, and on disability. Capturing and measuring these differences is the purpose of HRQOL assessment.

3.1.1 HRQOL Measurement

HROQL instruments can be classified into three main types: global, generic, and specific[16]. Global measures consist of a single question or score used to summarize overall quality of life. Often consisting of simple questions like "How is your quality of life?" these measures, although easy to administer and report, are often insensitive to smaller changes in quality of life and do not provide any information on specific areas of dysfunction[17]. Generic and specific instruments are questionnaires containing items that are grouped into domains. A domain or dimension is a specific area of experience/behaviour that the instrument is attempting to measure[15]. The items (questions) forming the individual domains are combined into scores representing each domain, thus allowing the researcher the ability to assess the impact of a therapy or disease on a specific domain. These domain scores are then combined to provide a summary score for that patient's HRQOL.

The classic example of a generic measure is the Medical Outcomes Survey Study 36-Item Short Form (SF-36)[18]. The SF-36 is a self-administered health survey composed of 36 items organized among 8 domains: bodily pain, general health, mental health, physical functioning, role-emotional, role-physical, social functioning, and vitality. The resulting score ranges from 0 (worst) to 100 (best). The advantages of such a scoring system lie in its applicability across patient populations and disease states.

Another type of generic instrument is one that measures *utility*, which is defined as a patient's preference for a specific disease state and/or treatment[19]. These measures

are rooted in decision theory and are typically used in economic analyses as they summarize HRQOL into a single number, usually from 0 (death) to 1 (perfect health). They can be combined with cost data to produce cost-utility analyses and are useful when evaluating health care programmes. Although useful, utility measures are often unresponsive to subtler changes in HRQOL and they do not show in which domain improvements or deteriorations occur[15].

Bernklev et al showed that when the SF-36 was applied to patients with ulcerative colitis, scores were significantly lower in 6 of the 8 domains when compared to normal population values[4]. Although useful in patients with ulcerative colitis, generic measures such as the SF-36 have been criticized for their lack of responsiveness, namely the ability to detect smaller changes in HRQOL related to disease activity or therapy over time[4,15,20]. To overcome this limitation, disease specific instruments have been developed to detect smaller yet clinically meaningful changes in HRQOL among patients with inflammatory bowel disease. The most commonly used disease specific instrument is the Inflammatory Bowel Disease Questionnaire (IBDQ)[21]. The IBDQ is an interviewer or self-administered questionnaire consisting of 32 questions organized along 4 domains: bowel symptoms, emotional functioning, social functioning and systemic symptoms, with each question being scored 1-7 resulting in a range of 32-224; with higher scores indicative of better HRQOL. The recommended approach is to utilize both a generic measure and a disease specific measure when evaluating the impact of a disease or therapy on HRQOL[4, 15, 17, 20]. Table 3.1 summarizes the most common instruments used in evaluating quality of life in inflammatory disease patients.

Table 3.1 Quality of Life Instruments Used in Ulcerative Colitis

Instrument	Items/Domains	Scoring
Generic		
SF-36[18]	36 questions organized into 8 domains: bodily pain, general health, mental health, physical functioning, role-emotional, role-physical, social functioning, and vitality.	0 (worst)-100 (best)
Sickness impact profile (SIP)[22]	136 questions evaluating every day activities among 12 categories: sleep and rest, emotional behaviour, body care, home management, mobility, social interaction, ambulation, alertness, communication, work, recreation, eating, these are further grouped along 2 domains, physical and psychosocial.	0 (most dysfunction)-100 (no dysfunction)
Utility		
Time Trade-Off Technique (TTOT)[23]	Based on standard gamble theory, patients are asked to trade-off time spent in a disease state with time spent being perfectly healthy, the resulting point of indifference (amount of time being healthy equivalent to normal life span in disease state) is translated into an index between 0-1.	0 (death) − 1.0 (perfect health)
Disease Specific		
Inflammatory Bowel Disease Questionnaire (IBDQ)[21]	32 question interviewer or self-administered questionnaire evaluating 4 domains: bowel symptoms, emotional function, social function, systemic symptoms.	Each question (1-7), 32-224 total score (higher score = better HRQOL)
Rating Form for IBD Patient Concerns (RFIPC)[24]	25 questions evaluating 5 domains: impact of disease, sexual intimacy, complications of disease, body stigma.	0-100 (higher score = worse HRQOL)

3.1.2 Characteristics of HRQOL Instruments

A methodologically robust HRQOL instrument must at the very least measure what it is intended to measure, namely quality of life. The difficulty arises as no "gold standard" exists for the measurement of quality of life[15], thus newly developed instruments cannot simply be validated by a comparison to a gold standard. To overcome this issue, concepts surrounding "surrogate" measures of validity have been borrowed from the psychological literature and applied to the validation of instruments intended to measure HRQOL. *Face validity* implies that an instrument appears to measure what it is intended to measure, while *content validity* refers to whether an instrument comprehensively examines the domains of interest relating to the intended concept to be measured[25]. These aspects of validity are not quantitatively evaluated, rather they are the result of careful review and consideration of the items within the instrument often by a panel of experts or patient focus groups[16]. *Construct validity* refers to how an instrument measures or behaves in relation to the theoretical construct it is supposed to measure[25]. It is evaluated by comparing changes in the instrument to changes in some other marker of disease, seeing if it behaves as predicted based on its theoretical construct. For example, an instrument used to measure pain (its theoretical construct) should correlate with changes in the amount of pain medication used. *Criterion validity* refers to an instruments ability to relate to a similar questionnaire intended to measure similar domains[16]. For example, a new disease specific measure of HRQOL could be compared to an established reference, such as the IBDQ, to see if the two are congruent. For a new instrument to be

deemed valid, it should satisfy these validity concepts. Table 3.2 summarizes properties of methodologically sound HRQOL measures.

Table 3.2 Desirable Properties of HRQOL Measures.

Property	Concept
Validity	
Face validity	Instrument evaluates intended concept
Content validity	Instrument is representative of all areas of interest being made up of multiple domains comprehensively representing the concept being studied
Construct validity	Instrument behaves as predicted by its theoretical construct when compared to some other marker of disease or therapy
Criterion validity	Instrument behaves congruently when compared with some accepted reference standard that measures similar concepts
Reliability	
Test-retest reliability	Instrument should have consistent results when applied repeatedly to the same patient and variation between patients should be greater than variability within patients
Internal Consistency	Items within a domain should correlate with each other

An instrument must not only be valid but must also display reliability when repeatedly applied to the same patients (test-retest reliability), have internal consistency among its various domains, and be responsive to clinically meaningful changes in HRQOL[15-17]. In a systematic review of instruments used for the measurement of HRQOL among patients with inflammatory bowel disease, Pallis et al identified two disease specific measures, the IBDQ and the RFIPC that have been shown to be valid and reliable[26]. As part of the systematic review of studies comparing HRQOL between

patients with an IPAA and patients with an ileostomy, we sought not only to summarize their results but also to evaluate whether they had measured HRQOL using a validated instrument.

3.2 Methods

Search Strategy

The details of the search strategy are outlined in chapter two of the thesis. Given the smaller number of studies in this group we did not limit ourselves to studies with at least 100 patients, but rather included all studies that compared health-related quality of life between patients undergoing IPAA or ileostomy. All titles and abstracts were independently reviewed by two reviewers, and any study that either reviewer deemed as potentially eligible was selected for full text review. Study inclusion was then assessed independently with any disagreement resolved by consensus. Specific study inclusion criteria are detailed in chapter two of this work.

Data Extraction

All information was extracted independently by two reviewers with any disagreements resolved by consensus. Data pertaining to details about the patients (age, sex), intervention (IPAA or ileostomy, complication rate), length of follow-up, and quality of life measures used were extracted. Numerical results of the various HRQOL instruments were also extracted along with their statistical significance (p-value) and the conclusions of the authors.

Quality Assessment

The method of assessment and justification for study quality evaluation is also found in chapter two of this work. However, this was expanded for the quality of life

studies to include an assessment of the validity of the instruments used in each study along the criteria in Table 3.2. HRQOL measures were evaluated based on whether the authors indicated in their study, or made reference to other studies, where the validity and reliability of their chosen HRQOL instrument had been established. Instruments were considered to have *face validity* if some description of the method used to decide on what elements to include in the measure were included in the work or in the references; while instruments were considered to have *content validity* if they were made up of multi-domain scores comprehensively covering the concept of interest. *Construct validity* was established if the authors described or made reference to studies that compared the instrument to some marker of disease or therapy. *Criterion validity* was established if the instrument was compared to some other established HRQOL measure. Where applicable the validation references were extracted. Instruments were considered to be overall valid if the authors displayed or made reference to the demonstration of construct and/or criterion validity, as these are the most rigorous methods of establishing validity[15].

Analysis

Although we had originally intended to meta-analyze the overall scores and domain specific scores of the included studies using weighted mean difference[27], where the difference between two groups is adjusted for by study size. We deemed that there was too much heterogeneity across studies in terms of different HRQOL instruments and the way the results were reported (some mean, some median) to allow for quantitative analysis. Instead, the individual study results are presented in a table with the conclusions reached by the authors of the studies.

3.3 Results

We identified 9 studies that compared HRQOL between patients with ulcerative colitis that had undergone either an ileal pouch-anal anastomosis procedure or an ileostomy. Agreement between reviewers for this subset of studies was excellent, with no disagreements about study inclusion (*kappa* = 1.0). Table 3.3 summarizes the study characteristics of included studies.

3.3.1 Quality of Included Studies

The quality of the studies varied widely with only three studies including consecutive patients and only two being prospective. Two studies adjusted for confounding, one in their analysis using a logistic regression, and the other in their design through matching patients from both groups for known confounders of HRQOL. Losses to follow-up, or in this case response rates to HRQOL questionnaires, were generally poor with all but three studies having >20% non-response rates. Table 3.4 summarizes the differences in study quality.

3.3.2 Validity of HRQOL Instruments Used

Of the included studies, 5 used validated measures of HRQOL, while four studies used non-validated measures. Three studies used the validated, generic SF-36 measure, while three studies utilized the validated, disease-specific IBDQ measure. Of the non-validated measures, most were global assessments based on a yes/no answer to a question related to either social restriction or overall satisfaction. Liddell et al used a self-developed score measure to assess patient satisfaction[28]. This assessed the degree of improvement with surgery over eight domains: social activities, sports activities,

housework, recreation, family relationships, sex, travel, and work. Although this measure met the criteria for face and content validity, no mention of methods to test construct or criterion validity were described. In a similar self-developed, non-validated score based instrument, Pemberton et al used a questionnaire consisting of seven domains: sports, sexual life, social activities, recreation, work around the house, family relationships, and travel; to assess the impact of surgery on restrictions in each domain[29]. Again, construct and criterion validity were not assessed. McLeod et al utilized two validated utility measures to assess the impact of each procedure on overall quality of life, as well as a validated generic measure, the Sickness Impact Profile[30].

3.3.3 Comparison of IPAA to Ileostomy Patients

Global instruments

Studies using global measures to compare HRQL between ileostomy and IPAA patients found there were no significant difference between patients overall satisfaction (95 vs 93%)[29], ability to return to work or school (98 vs 94%)[29], and overall quality of life (87 vs 93%)[31]. Similar results were described using two validated utility measures with no difference between groups[30]. Emblem et al described significantly more societal restriction among ileostomy patients using a non-validated questionnaire (67% vs 0%)[32].

Generic instruments

Of the three studies using the SF-36, no difference in overall scores was found between the two groups[3, 33, 34]. The only domain-specific difference was described by Nordin et al who found worse social functioning among the IPAA patients[3]. McLeod et al

found similar results with no difference in overall scores using the Sickness Impact Profile[30]. Two non-validated generic instruments showed mixed results. Liddell's Lifestyle Satisfaction Score failed to detect a difference between the two groups, either in its summative score or in the individual domain scores[28]. In contrast, Pemberton's Performance Score, which contained similar elements to Liddell's score, found significant worse performance scores among ileostomy patients among all seven domains (sports, sexual life, social activities, recreation, work around the house, family relationships, and travel)[29].

Disease-specific instruments

Of the three studies using the IBDQ, no differences in overall scores were found between the two groups[3, 34, 35]. Only one study identified a difference in domain specific scores, Nordin et al described worse social functioning and systemic symptoms among the IPAA patients[3]. O'Bichere et al using a self-developed, non-validated, disease specific visual analogue scale (VAS) found IPAA patient to have worse altered bowel habits and more restrictions on diet than patients with ileostomies; while ileostomy patients had worse body image[33]. Table 3.6 summarizes the study results and conclusions.

3.4 Discussion

Health-related quality of life is a measure of a patient's perception of the impact a disease or its therapy has on their illness experience and functional status[36]. We identified nine studies that compared HRQOL between ileostomy and IPAA patients. No study identified an overall difference in quality of life between the two groups. Overall markers of quality of life, whether they are global, non-validated, generic, or disease specific, all indicate that patients with ulcerative colitis who undergo proctocolectomy have good

HRQOL regardless of which reconstructive option they undergo (ileostomy or IPAA). This is in keeping with the concept that removal of the diseased colon is what improves a patient's quality of life following surgery, not the restoration of anal defecation.

Although the restoration of anal defection via an IPAA has been perceived to result in an improved quality of life when compared to an ileostomy, as indicated by some modern narrative reviews[37, 38], this claim is not substantiated by a critical review of the literature. In fact, older literature indicates a high degree of satisfaction among patients with ileostomies. In a survey of 273 patients with ileostomies, Roy et al reported that 92% perceived themselves to have a normal lifestyle, and 89% indicated they had good or excellent health[39]. In a similar survey of 273 patients with ileostomies from the Cleveland Clinic, 74% of patients reported that they had normal lives[40]. Further evidence that removal of the diseased colon is the key to good post-operative quality of life comes from a study by Weinryb et al where patients having undergone a staged IPAA had their quality of life assessed before and after their temporary ileostomies were closed. Using a validated generic measure, the Psychological Adjustment to Illness Scale (PAIS)[41], the authors found no further improvement in HRQOL following closure of ileostomy[42, 43].

Studies have documented an improvement in HRQOL following proctocolectomy in patients with ulcerative colitis primarily related to control of their symptoms and disease[12, 30, 44]. Of note, these benefits are less apparent among patients with familial adenomatous polyposis (FAP) who undergo IPAA. FAP is an inherited disorder characterized by the development of hundreds of polyps and a high risk of colon cancer, often warranting a prophylactic proctocolectomy as most patients will ultimately develop colon cancer [45]. These patients often receive an IPAA but they are not generally

symptomatic or ill prior to the procedure, unlike ulcerative colitis patients. Studies comparing postoperative quality of life among FAP and ulcerative colitis patients have consistently found a worse postoperative quality of life among FAP patients[46, 47]. In a study of 64 patients, 10 of whom had FAP, HRQOL assessed by the Cleveland Clinic Global Quality of life scale[8] found significantly worse quality of life among FAP patients[46], despite improved functional results in the FAP group.

Although we found no overall differences in HRQOL, some domain/item specific differences were observed between IPAA and ileostomy patients. Pemberton et al using a self-developed performance status score found more functional restriction among patients with ileostomies, particularly among the sexual activity, sports, social activities, and travel domains[29]. In contrast, Nordin et al, using the well validated IBDQ and SF-36 found worse social functioning among the IPAA patients on both items[3]. These disparate findings may be explained by the effects of morbidity on quality of life. In Pemberton's study, patients with ileosotomies had a much higher morbidity (complication) rate (22% vs 11%), which likely contributed to their worse functioning. The use of different instruments may also explain the contrasting results, although this is difficult to assess given the lack of validation of Pemberton's performance score. O'Bichere also found worse domain specific scores with IPAA patients indicating that their procedure more negatively impacted on their bowel habits and diet when compared to ileostomy patients[33]. However, this was based on a non-validated self-developed score, and thus it is difficult to properly compare these results to those obtained using validated instruments. No study using a validated generic or disease specific instrument identified greater functional restriction among patients with ileostomies.

One consistent finding, however, was the reduced body image associated with an ileostomy. O'Bichere found a reduced body image among ileostomy patients when measured on their self-developed visual analogue score, although this did not result in a reduced overall quality of life when combined to produce a summative score, as it was offset by problems with pouch functioning among the IPAA patients[33]. Camilleri-Brennan, using a self-developed, non-validated questionnaire also found reduced body image among patients with ileostomies[34]. Liddell et al using a validated multidimensional Body Self-Relations Questionnaire[48] also found reduced body image among patients with ileostomies[28]. Despite these findings, no study identified any overall differences in quality of life, indicating that the overall impact of reduced body image is unlikely to be of any great functional consequence to these patients.

Ultimately, any systematic review is limited by the quality of its included studies. The quality of the nine studies varied widely, not only in their design (Table 3.4), but also in the quality of their method of HRQOL assessment (Table 3.5). These differences made comparisons between studies difficult to interpret. The most important aspect of quality is the use of validated measures of HRQOL. Statistical tests of the results of non-validated instruments are of little value and hazardous to interpret[36]. The studies of the highest methodological quality used both a validated generic and a validated disease specific instrument in their assessment of HRQOL; both identified no difference in HRQOL between IPAA and ileostomy patients. In the remaining studies, one used a validated generic measure and two validated utility measures, one used a validated generic measure combined with a non-validated disease specific instrument, one used a validated disease specific instrument only, and 4 used non-validated global measures. The design of studies

varied greatly with only three being prospective and six being retrospective. Only two

studies adjusted for confounding. Pemberton et al adjusted the results of their

performance score using a logistic regression accounting for differences in age, sex,

duration of disease, and re-operation, although there performance score was not a

validated measure[29]. Camilleri-Brennan's study was of the highest methodologic quality

as they combined a prospective design, adjustment for confounding, standardized follow-

up, and validated HRQL assessment (generic and disease specific)[34]. They matched

patients in both groups for age, sex, socioeconomic status, and time since surgery and

found no difference in HRQOL in either the generic or disease-specific instruments.

All but one study had suboptimal response rates to the questionnaires, with rates

ranging from 98% to 58.1%. This is an important consideration as non-responders are

often different in terms of characteristics than responders, and this can introduce bias into

the results[49]. The only study to compare responders to non-responders identified no major

differences in demographics or complications between the two groups[31], thus the impact

of this potential bias is difficult to determine.

The studies were generally limited by their small sample size with only one study

containing greater than 100 patients per group. This may have resulted in under-powered

comparisons. One way to overcome this would have been a quantitative meta-analysis of

the results. This was not possible as the studies used different measures of HRQOL; and

in the studies that did use similar measures, the results were reported differently (mean vs

median), not allowing for meta-analysis. One approach would have been to combine the

results of different measures through standardization, although this approach has been

criticised for introducing bias as the most responsive instruments will carry

disproportionately more weight in the analysis[50]. Despite small numbers, disease-specific measures such as the IBDQ have been shown to be responsive enough to be suitable for even small trials (n=20)[36].

This is the only systematic review looking specifically at the question of whether IPAA patients have improved health-related quality of life when compared to patients with ileostomies. Despite its systematic nature, this review does have several limitations. The first is the variable quality of the studies as discussed above. The second is the inability to quantitatively combine the results into a meta-analysis. Although this may have improved the power of the comparison, it may have introduced bias as the studies were fairly heterogeneous in terms of their clinical characteristics (morbidity rates), methods of HRQL assessment, length of follow-up, and methodological quality. Thirdly, no specific measures were taken to account for publication bias. Publication bias usually results from not including non-published studies that are more likely to have non-significant results[51]. This is unlikely to be a factor as the major substantive conclusion of this review is that no difference exists between the groups. A final limitation is the inclusion of English-only language studies, the justification for and rationale can be found in chapter two of this work.

Although limited by variable study quality and small sample sizes, the current literature does not support the assumption that the more advanced IPAA procedure leads to an increase in quality of life when compared to the conventional ileostomy. Both appear equivalent in terms of overall quality of life, although ileostomy patients have poorer body image. These findings provide further rationale and justification for the development of a patient decision aid to help patients decide between the two

reconstructive options. This literature supports the concept that patients who select a certain option are satisfied with their choice and generally enjoy a good HRQOL. Despite high complication rates following IPAA, Skarsgard et al showed that 92% of patients would choose to undergo a pouch procedure again[52]. Thus empowering and facilitating this choice, rather than recommending one option over the other is the right way to approach the therapeutic decision between an IPAA and an ileostomy.

TABLE 3.3. Quality of Life Study Characteristics

Study (author/year)	Country	HRQOL measure	Groups	N	Age (mean, range, yrs)	Male (%)	Morbidity rate (%)	Follow-up (mean, months)
Emblem (1988)[32]	Norway	Social restriction	IPAA	19	27 (23-38)	53	21	48
			Ileostomy	35	30 (26-35)	60	71	58
Pemberton (1989)[29]	USA	Overall satisfaction, return to work or school, Performance status	IPAA	298	32*	51	11	47*
			Ileostomy	406	38	59	22	104
McLeod (1991)[30]	Canada	Time trade-off (TTOT) Direct questioning of objectives (DQO) Sickness-impact profile (SIP)	IPAA	37	36 ± 9	49	8.1†	NR
			Ileostomy	28	39 ± 13	54	18	NR
Liddell (1995)[28]	Canada	Lifestyle satisfaction	IPAA	25	33.2 ± 7	40	NR	40
			Ileostomy	10	51 ± 14	40	NR	47
Jimmo (1998)[35]	USA	Inflammatory Bowel Disease Questionnaire (IBDQ)	IPAA	55	31	45	49	12
			Ileostomy	12	52	60	8	12
O'Bichere (2000)[33]	UK	Visual analogue scale (VAS) Short-Form 36 (SF-36)	IPAA	30				
			Ileostomy	30	43 (22-71)‡	44	NR	13

62

Seidel (2000)[31]	USA	Overall quality of life	IPAA	55	31.2 ± 1.3	55	63	
			Ileostomy	31	44.8 ± 3.7	48	16	30.6 ± 3.5‡
Nordin (2002)[3]	Sweden	SF-36 IBDQ	IPAA	57				
			Ileostomy	42	46 (20-70)	48	NR	NR
Camilleri-Brennan (2003)[34]	Scotland	SF-36 IBDQ	IPAA	19	41*	63	21.1	41*
			Ileostomy	19	41	63	42.1	43

* median; † rate of re-operation; ‡for both groups combined; NR not recorded

TABLE 3.4 Study Quality Assessment

Study (author/year)	Consecutive patients	Study type	Adjustment for confounding	Response Rate	Validated QOL measure
Emblem (1988)[32]	No	Retrospective	No	100%	No
Pemberton (1989)[29]	Yes	Retrospective	Yes[2]	81%	No
McLeod (1991)[30]	No	Retrospective	No	98%	Yes
Liddell (1995)[28]	No	Retrospective	No	87.5%	No
Jimmo (1998)[35]	Yes	Prospective	No	79%	Yes
O'Bichere (2000)[33]	No	Retrospective	No	68.9%	Yes
Seidel (2000)[31]	Yes	Retrospective	No	58.1%	No
Nordin (2002)[3]	No	Retrospective	No	69.3%	Yes
Camilleri-Brennan (2003)[34]	No	Prospective	Yes[3]	76%	Yes

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[2] Pemberton et al adjusted for confounding in their analysis using a logistic regression for performance scores, adjusting for age, sex, duration of disease, and subsequent re-operation.

[3] Camilleri-Brennan et al adjusted for confounding in their design by matching the two groups for age, sex, time since surgery, and socioeconomic status,

TABLE 3.5. Properties of Quality of Life Instruments

Study (author/year)	HRQOL measure (type)	Face validity	Content validity	Construct validity	Criterion validity	Internal consistency	Reliability	Validation references
Emblem (1988)[32]	Societal restriction (global)	No	No	No	No	NA	No	-
Pemberton (1989)[29]	Overall satisfaction, Return to work or school,	No	No	No	No	NA	No	-
	Performance status (generic)	Yes	Yes	No	No	No	No	
McLeod (1991)[30]	TTOT (utility)	Yes	Yes	Yes	Yes	NA	Yes	Bergner et al[22] Churchill et al[53]
	DQO (utility)	Yes	Yes	Yes	Yes	NA	Yes	Detsky et al[54] Torrance et al[23]
	SIP (generic) (range 0-100)	Yes	Yes	Yes	Yes	Yes	Yes	
Liddell (1995)[28]	Lifestyle satisfaction (generic)	Yes	Yes	No	No	No	No	-
Jimmo (1998)[35]	IBDQ (disease specific)	Yes	Yes	Yes	Yes	Yes	Yes	Guyatt et al[21] Irvine et al[25]
O'Bichere (2000)[33]	SF-36 (generic)	Yes	Yes	Yes	Yes	Yes	Yes	Ware et al[18] McHorney et al[55, 56]
	VAS (disease-specific)	No	No	No	No	No	No	
Seidel (2000)[31]	Overall quality of life (global)	No	No	No	No	No	No	-
Nordin (2002)[3]	SF-36 (generic)	Yes	Yes	Yes	Yes	Yes	Yes	Ware et al[18]McHorney et al[55, 56]
	IBDQ (disease specific)	Yes	Yes	Yes	Yes	Yes	Yes	Guyatt et al[21] Irvine et al[25]
Camilleri-Brennan (2003)[34]	SF-36 (generic) IBDQ (disease-specific)	Yes Yes	Yes Yes	Yes Yes	Yes Yes	Yes Yes	Yes Yes	Ware et al[18]McHorney et al[55, 56] Guyatt et al[21] Irvine et al[25]

TABLE 3.6 Quality of Life Study Results

Study (author/year)	Groups (n)	QOL measure	Numerical results		p-value	Conclusions
			IPPA	Ileostomy		
Emblem (1988)[32]	IPAA (19) Ileostomy (35)	Societal restriction (%yes)	0%	67%	<0.01	Ileostomy patients suffered greater social restriction then IPAA patients
Pemberton (1989)[29]	IPAA (298) Ileostomy (496)	Overall satisfaction (%yes) Return to work or school (%yes) Performance score[1]	95% 98% -	93% 94% -	NS NS <0.05	Overall satisfaction was similar between the two groups although IPAA patients had improved performance scores when compared to ileostomy patients[4]
McLeod (1991)[30]	IPAA (37) Ileostomy (28)	TTOT (0-1.0) (mean ±SD) DQO (0-1.0) (mean ±SD) SIP (0-100) (mean ±SD)	0.95 ± 0.15 0.87 ± 0.18 1.2 ± 2.3	0.97 ± 0.08 0.89 ± 0.15 3.1 ± 5.0	NS NS NS	No difference in QOL using two utility measures and one generic measure between the two groups. Even a subgroup analysis of ileostomy patients contemplating a change to IPAA showed no difference.
Liddell (1995)[28]	IPAA (25) Ileostomy (10)	Lifestyle Satisfaction[5] Overall satisfaction (1-7) (mean ± SD)	 5.48 ± 1.56	 5.7 ± 1.34	 NS	No difference in overall satisfaction between the two groups. Comparison of the seven sub-categories[2] failed to reveal any differences as well.

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[4] Pemberton et al used a self- developed, un-validated, performance score measure as a way to determine the impact of each surgical procedure on daily life. It consisted of seven categories (sports, sexual life, social activities, recreation, work around the house, family relationships, and travel) each assessed with a 5-point Likert scale. The results were only presented graphically, thus they were not extractable. In each category, IPAA patients showed significantly less restriction than ileostomy patients.

[5] Liddell et al used a self-developed, un-validated score-based questionnaire to assess patient satisfaction. Eight domains and an overall assessment were explored: social activities, sports activities, housework, recreation, family relationships, sex, travel, and work; and each was given a score based on a 7-point Likert scale (markedly worse to marked improvement).

Jimmo (1998)[35]	IPAA (55) Ileostomy (12)	IBDQ (32-224) (mean ±SD)	205 ± 20^{6}	200 ± 25	0.49	No difference in disease-specific quality of life between the two groups. No difference demonstrated when individual categories of IBDQ were compared
O'Bichere (2000)[33]	IPAA (30) Ileostomy (30)	SF-36 (0-100) (median) Health perception Physical functioning Role-physical Role-emotional Social functioning Mental Health Bodily pain Energy/vitality VAS (1-10)^{7} (median) Body image Altered bowel emptying Odour Noise Sexual relationship Clothes Diet	 57 90 88 100 88 68 90 43 5 8 5 5.5 5 3.5 5.5	 55 80 75 100 88 76 80 53 8 5 8 6 7 3 2	 NS NS NS NS NS NS NS NS NS <0.05 NS NS NS NS <0.05	No difference was found in HRQOL using the SF-36 instrument between the two groups. The negative impact altered bowel habits and problems with pouch functioning are highlighted by the differences in the VAS domain of bowel emptying. While the negative effects of the ileosotomy on body image are also evident as these patients scored worse on the VAS.
Seidel (2000)[31]	IPAA (55) Ileostomy (31)	Overall quality of life Better since operation (always %)	87	93	NS	No difference between groups in overall quality of life.
Nordin (2002)[3]	IPAA (57) Ileostomy (42)	SF-36 (0-100) (mean) Overall health Physical functioning Role-physical Role-emotional Social functioning Mental Health	 NR NR NR NR 70.2 NR	 NR NR NR NR 89.3 NR	 <0.05 	Patients with IPAA actually scored worse on some domains of both the generic and disease specific measures of HRQL. IPAA patients had worse social functioning, more bowel symptoms, and worse emotional functioning than patients with ileostomies. There were no differences in the remaining domains of

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[6] Values extrapolated from figure.

[7] O'Bichere et al used a self-developed, non-validated 10-point visual analogue scale to assess how problematic patients saw the surgery in relation to each domain: body image, altered bowel emptying, odour, noise, sexual relationship, clothes, diet. Each was given a score from 1 (least problematic) to 10 (most problematic).

			NR	NR		either instrument, although numerical results were not reported.
		Bodily pain	NR	NR		
		Energy/vitality	NR	NR		
		IBDQ (32-224) (mean)				
		Bowel symptoms	NR	NR		
		Systemic symptoms	54.4	63	<0.01	
		Emotional functioning	NR	NR		
		Social functioning	64.8	72.2	<0.01	
Camilleri-Brennan (2003)[34]	IPAA (19) Ileostomy (19)	SF-36 (0-100) (median)				There were no significant differences in overall or domain specific measures of HRQOL between the two groups. Although a small sample size, the study used matching to control for confounding adding methodologic rigor to their results. Body image was also explored with a non-validated, self-developed measure which did show inferior body image among patients with ileostomies.
		Overall health	62	77	0.70	
		Physical functioning	95	90	0.24	
		Role-physical	93.8	100	0.60	
		Role-emotional	100	100	0.57	
		Social functioning	100	100	0.81	
		Mental Health	85	75	0.14	
		Bodily pain	88.9	88.9	0.21	
		Energy/vitality	62.5	77	0.49	
		IBDQ (32-224) (median)				
		Global score	85.4	80.7	0.56	
		Bowel symptoms	81.7	80	0.32	
		Systemic symptoms	80	83.3	0.25	
		Emotional functioning	84.7	80.6	0.76	
		Social functioning	95.8	91.7	0.56	

TTOT=Time Trade-Off Technique; DQO= Direct Questioning of Objectives; SIP = Sickness Impact Profile; NS = non-significant, NR = not recorded

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CHAPTER FOUR – A SYSTEMATIC REVIEW AND META-REGRESSION OF OUTCOMES FOLLOWING ILEAL POUCH-ANAL ANASTOMOSIS

4.0 Introduction

Patients with ulcerative colitis who wish to avoid a permanent ileostomy have the option to undergo a restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA). This technique involves the formation of a reservoir using the small bowel (ileum) and joining it to the anus to form a neo-rectum. Originally described by Parks and Nicholls in 1978[1], the procedure has undergone many modifications and in its most common form consists of a two-stage procedure where the colon and rectum is removed and the pouch created, and protected with a diverting ileostomy that diverts the fecal stream away from the pouch allowing it to heal[2]. Patients then undergo a closure of the ileostomy at a second operation. It is important to note that this procedure does not improve the control of ulcerative colitis, rather it is a procedure aimed at improving a patient's quality of life and day to day functioning through the avoidance of a stoma.

As explored in chapter three of this work, there is no conclusive evidence that it universally leads to better health-related quality of life when compared to the conventional proctocolectomy and ileostomy. Rather the decision to undergo a restorative proctocolectomy should be made by the patient and be in line with their values and expectations. In order to facilitate this decision, patients must be informed about the risks of serious complications following the procedure. In order to provide estimates of these complications for inclusion into our decision aid, a systematic review and meta-analysis of serious outcomes following IPAA was conducted. One previous meta-analysis published by Hueting et al in 2005 had several limitations[3]. They did not explore any study quality items, no formal tests of heterogeneity were conducted, there were minimal

efforts to explore heterogeneity among studies, no assessment of publication bias was undertaken, and the review was dated as it only included studies published up to 2000. We conducted an updated meta-analysis and took measures to explore and quantify heterogeneity among studies.

4.1 Methods

Search Strategy

The details of the search strategy are presented in chapter two of this work, along with the justification and listing of the specific inclusion criteria. Briefly, we included studies of at least 100 patients that reported on outcomes of interest regardless of pouch type, number of stages, and length of follow-up. All titles and abstracts were independently reviewed by two reviewers, and any study that either reviewer deemed as potentially eligible was selected for full text review. Study inclusion was then assessed independently with any disagreement resolved by consensus. When conducting our review, we followed the guidelines set out by the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[4] and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[5] groups.

Data Extraction

All information was extracted independently by two reviewers with any disagreements resolved by consensus using standardized, custom designed, data-abstraction sheets. Study characteristics including size; location; time period of patient enrollment; length of follow-up; mean age; proportion with Crohn's, FAP, or indeterminate colitis; proportion with prior subtotal colectomy; proportion of stapled

anastomosis; proportion with J-pouch configuration; and proportion with diverting loop-ileostomy were abstracted. Outcomes of interest included pouch failure (pouch excision or permanent diverting ileostomy,), pelvic sepsis (pelvic abscess, anastomotic leakage, or perineal wound infection), pouch-fistula (any fistula involving the pouch), stricture (anastomotic stricture requiring dilatation), small bowel obstruction (requiring laparotomy), and sexual dysfunction (erection disorder or dyspareunia). Functional results were also extracted including mean number of bowel movements per day, mean number of bowel movements at night, proportion with significant fecal incontinence, fecal urgency (inability to defer defecation), proportion with daily pad use, and proportion requiring daily anti-diarrheal medication use.

Quality Criteria

The justification for and rationale behind the selection of quality criteria is discussed in depth in chapter two of this work, but a brief synopsis follows here. Although many tools and scales exist for the assessment of quality criteria of observational studies, no one tool can be recommended above others as there is no empirical evidence linking specific observational study design elements to validity[6, 7]. With that in mind, specific elements of study design reflective of quality were investigated individually with regards to influence on outcome measures rather than using summary scores of quality[8]. The study quality criteria examined included: whether or not the patients represented a group of consecutive patients having surgery over a pre-specified time period, whether the authors used clearly defined outcome criteria, whether the study was retrospective or prospective, proportion loss to follow-up, and whether the authors employed a standardized follow-up procedure.

Meta-Analysis

Each study estimate of a given outcome was recorded and its 95% confidence interval was determined using Wilson's score method[9]. In order to combine the proportions from individual studies, we converted the individual proportions into odds[10], and the odds were transformed into the log scale using equation 4.1:

$\ln(\text{odds}) = \ln$ (no of patients having event/ no of patients not having event)   (4.1)

This allowed us to generate a variance term which was used in the weighting of studies for the meta-analysis (equation 4.2):

$\text{var} \ln(\text{odds}) = 1/\text{no of patients having event} + 1/\text{no of patients not having event}$[10]   (4.2).

Meta-analysis was then carried out using individual study proportions converted to the $\ln(\text{odds})$ scale according to the random-effects model of DerSimonian and Laird[11], accounting for both within-study variance and between-study variance. This model assumes that the outcome measures of each study come from a random distribution of outcomes, with the weighting of studies based on the reciprocal of the sum of between study variance and within study variance. The statistical package, STATA version 10 (*Stata inc,* Texas, US, 2008) using the procedures *meta* and *metan* were used to meta-analyse the data as described by Sharp[12]. This procedure estimates the between-study variance using the non-iterative weighted method of DerSimonian and Laird[11]. Pooled results were converted back to the proportion scale and presented along with their 95% confidence interval. In cases where the study had no events, a continuity correction factor

was added (0.5) in order to generate an outcome measure for the meta-analysis as ln(0) is not a real number. Adding a continuity correction is preferred over excluding studies with zero events[13]. Each outcome was also graphically summarized using Forrest plots. The possibility of publication bias was explored using funnel plots of the individual outcomes, looking for asymmetry amongst the smaller trials. This was done assuming smaller trials might be more apt to get published if they have "better" results, i.e. lower rates of complications following IPAA.

Heterogeneity

Heterogeneity was statistically assessed for each outcome using the Cochran's Q chi-squared test which is calculated by adding together the squared deviations of each study's outcome from the overall pooled outcome, and then adjusting each deviation by the study's weight used in the meta-analysis[14]. This statistic, although widely used, is often under-powered[15, 16]. In an effort to improve the test`s power, some author have argued establishing a cut-off of 0.1 as the nominal level of significance for this test[17, 18]. However, we maintained a value of 0.05 for this analysis as we had a large number of studies which would improve its power. The degree of heterogeneity was also quantified using the I^2 statistic, which is the percentage of total variation across studies that is not explained by chance[19]. The resulting value ranges from 0 (no heterogeneity) to increasing proportions of non-chance related heterogeneity as the % I^2 increases.

Exploration of Heterogeneity

To explore the heterogeneity we conducted selective subgroup analyses on pre-specified study characteristics, namely, 85% or greater proportion of pouches created with J-configuration, studies with 100% diversion at the time of pouch creation, follow-up greater or equal to five years, and loss to follow-up of <10%. The most common pouch configuration in the modern era is the J-pouch[2, 20, 21] thus looking at studies that include a majority of patients with this pouch configuration is most relevant to the modern patient. While routine use of a diverting ileostomy has been linked to reduced septic complications following IPAA and has been adopted by most surgeons[22]. Longer follow-up has been linked to increased complication rates following IPAA as complications such as pouch failure and pouchitis tend to occur over the long-term[3], and losses to follow-up have been empirically linked to differences in outcome measures in meta-analyses of experimental literature[23]. Our other quality criteria, namely consecutive patients (protection against selection bias), outcome criteria definition, and standardized follow-up have not been shown in prior research to be linked with validity or outcome.

Each methodologic and study characteristic was systematically tested against the outcome for its contribution to study heterogeneity using univariable and multivariable meta-regression. Those factors that significantly contributed to heterogeneity amongst studies were then considered for subgroup analysis provided there was a plausible clinical or pathologic rationale. This last step was necessary to reduce concerns about multiple testing and data dredging where associations may arise purely from chance alone[24].

Meta-Regression

Meta-regression involves exploring the linear association between study level covariates and the pooled effect measure generated in the meta-analysis. It seeks to determine how much of the heterogeneity is explained by variations in a single or a set of given methodologic or study level factors[10]. It occurs at the study level with the outcome being the meta-analyzed variable (here the ln(odds) of each outcome), and the covariates, which include the study level factors (such as size, length of follow-up, etc).

Exploratory meta-regressions were undertaken to identify study level factors that significantly contributed to the between-study variability. Study level factors explored included methodologic criteria: consecutive patients, outcome definition, losses to follow-up, study type (retrospective vs prospective), standardized follow-up, and length of follow-up. The following study characteristics were also explored: mean age of patients, mid-point year of patient cohort, proportion of patients with Crohn's disease, proportion of patients with FAP, proportion of patients with indeterminate colitis, proportion undergoing diversion, proportion of stapled anastomoses, and proportion with j-pouch configuration. For each study level factor, the significance of its association with the outcome on the log scale and the proportion of outcome variability accounted for by the factor were reported. For those that significantly contributed to outcome heterogeneity, a plot of the study factor and the outcome on the log scale are presented with the symbol representing each study, proportionally sized to the weight of the study. Meta-regression was performed using the STATA command *metareg*, which carries out a random-effects meta-regression and estimates the between study variance using the iterative residual maximum likelihood method[12]. The use of a random-effects meta-

regression is preferred as fixed-effects meta-regression would only be appropriate if *all* the heterogeneity was explained by the covariates. This is generally not possible and the residual heterogeneity must be acknowledged in the analysis[24]. In order to undertake a random-effects meta-regression some estimate of residual between study variance must be generated. Multiple methods exist, some based on empirical Bayesian estimates, others on iterative restricted maximum likelihood estimates (REML). Iterative methods are preferred as they do not require any subjective assumptions about prior probabilities[24]. Only studies that reported on a given covariate (study factor) could contribute to the meta-regression.

4.2 Results

4.2.1 Study Selection

Our searches resulted in 3920 abstracts and titles, with 411 full-text papers retrieved for review and 67 studies ultimately met our inclusion criteria. There was good agreement beyond chance between the two independent reviewers for study inclusion ($k = 0.87$). The most common reason for exclusion were papers reporting on duplicate cohorts of patients who had been treated at the same institution over a similar time period (n=124). Other reasons for exclusion included studies with < 100 patients, review papers, papers reporting on sub-groups only, studies reporting on outcomes not related to our inclusion, and non-English language papers. Occasionally two papers from the same center were included if they reported on different outcomes or reported on patients from two non-overlapping time periods.

4.2.2 Study Description

The 67 studies included 21,882 patients treated in 19 different countries who were followed for a mean (SD) of 62.1 (34) months (range: 13-180 months). The studies reported on patients operated on from 1977 to 2005, with specific time span of cohorts differing from study to study (Table 4.1). The mean age at time of surgery was 34.9 years, ranging from 23.8 to 40 years (Table 4.2). Study size ranged from 100 to 1885 patients with an overall mean study size of 327 patients. Eighteen studies included patients with Crohn's disease, with proportions ranging from 0.16% to 24%, while 20 studies included patients with indeterminate colitis, ranging from 0.5% to 29.4%. Patients with FAP were included in 33 studies with proportions ranging from 2.3% to 16%. The rate of proximal diversion (loop ileostomy) at the time of pouch creation varied among studies with 28 studies reporting universal diversion with every patient, while the rates of diversion varied between 20% and 99.3% among the other studies. The rates of stapled-anastomosis also varied between 0% and 100%. The most common method of pouch construction was the J-pouch configuration, with 17 studies reporting exclusively on J-pouch patients. While the rates of J-pouch configuration varied between 3.1% and 99.5% among other studies.

4.2.3 Study Quality Assessment

Of the included studies, 25 (37%)were prospective, 42 (61%) included consecutive patients, 30 (44%) studies used standardized follow-up, and 51 (76%) studies used clearly defined outcomes to assess rates of complication, with 18 (27%) studies

using clearly defined outcome criteria for all their reported outcomes. Fifty two studies

(77.6%) reported losses to follow-up; the average loss to follow-up was 7.5% (range 0-

29%) and 36 studies reported less than 10% losses to follow-up.

Table 4.1 Characteristics of Studies Reporting on Outcomes Following IPAA

Author	Location	Years of Surgery	Consecutive Patients	Type of Study	Outcomes Defined	Standardized Follow-up
Fonkalsrud et al[25],1988	UCLA, US	1977-1988	No	Retrospective	None	No
Nicholls et al[26], 1989	St Marks, UK	1976-1986	Yes	Prospective	None	No
Pescatori and Mattana[27], 1990	Multicenter, Italy	1980-1989	No	Retrospective	Some	No
Wexner et al[28], 1990	Minnesota, US	1980-1988	No	Retrospective	None	No
Becker et al[29], 1991	Harvard, US	1982-1990	No	Prospective	Some	Yes
Harms et al[30], 1992	Wisconsin, US	1984-1991	No	Retrospective	Some	No
Fischer et al[31], 1993	Cincinnati, US	NR	Yes	Retrospective	Some	No
Mathey et al[32], 1993	Multicenter, Swiss	1980-1991	No	Retrospective	Some	No
Sagar et al[33], 1993	Leeds, UK	1980-1990	Yes	Prospective	None	No
Atkinson et al[34], 1994	Vancouver, Canada	1984-1992	Yes	Retrospective	None	No
Daude et al[35], 1994	Paris, France	1983-1991	No	Retrospective	Some	Yes
Hulten et al[36],1994	Goteborg, Sweden	1982-1992	No	Retrospective	Some	No
Lewis et al[37], 1994	London, UK	1983-1991	Yes	Retrospective	None	Yes
Gorfine et al[38], 1995	New York, US	1992-1994	Yes	Retrospective	Some	No
Hewett et al[39], 1995	Brisbane, Australia	1981-1993	Yes	Retrospective	None	No
Sitzmann et al[40], 1995	Baltimore, USA	1987-1992	Yes	Retrospective	Some	Yes
Stahlberg et al[41], 1996	Huddinge, Sweden	1980-1993	Yes	Prospective	All	Yes
McCourtney and Finlay[42],1997	Glasgow, Scotland	1988-1995	Yes	Retrospective	Some	Yes
Romanos et al[43], 1997	Oxford, UK	1983-1995	Yes	Retrospective	Some	Yes
Breen et al[44], 1998	Lahey Clinic, US	1980-1996	Yes	Prospective	All	Yes
Belliveau et al[45], 1999	Montreal, Canada	1981-1994	Yes	Retrospective	None	No
Fazio et al[46], 1999	Cleveland, US	1986-1997	Yes	Prospective	Some	Yes
Neilly et al[47], 1999	Auckland, NZ	1982-1997	No	Retrospective	None	Yes
Tiainen et al[48], 1999	Tampere, Finland	1985-1995	Yes	Retrospective	None	No
Young et al[49], 1999	Sydney, Australia	1984-1997	Yes	Retrospective	Some	No
Karlbom et al[50], 2000	Uppsala, Sweden	1983-1996	No	Retrospective	Some	Yes
Keighley et al[51], 2000	Birmingham, UK	1983-1999	Yes	Prospective	None	No
Mowschenson et al[52],2000	Boston, US	1989-1996	Yes	Prospective	Some	No
Simchuk and Thirlby[53], 2000	Seattle, US	1987-1996	Yes	Retrospective	Some	Yes
Sugerman et al[54], 2000	Richmond, US	1989-1999	Yes	Retrospective	Some	Yes
Blumberg et al[55], 2001	New Orleans, US	1982-1995	No	Retrospective	Some	No
Heuschen et al[56], 2001	Heidlberg, Germany	1982-1997	Yes	Prospective	All	Yes
Madiba and Bartolo[57], 2001	Edinburgh, Scotland	1990-1999	No	Prospective	All	Yes
Regimbeau et al[58], 2001	Paris, France	1984-1998	Yes	Retrospective	None	Yes
Dayton et al[59], 2002	Salt Lake City, US	1982-2001	Yes	Retrospective	Some	Yes
Heuschen et al[60], 2002	Heidlberg, Germany	1988-1999	Yes	Retrospective	Some	Yes
Lepisto et al[61], 2002	Helsinki, Finland	1985-1999	No	Retrospective	All	Yes
MacLean et al[62], 2002	Toronto, Canada	1981-1999	Yes	Prospective	All	Yes
Robb et al[63], 2002	Cincinnati, US	1978-2001	No	Retrospective	Some	No
Rudolph et al[64], 2002	Louisville, US	1991-1999	Yes	Prospective	Some	No
de Oca et al[65], 2003	Barcelona, Spain	1985-2000	No	Retrospective	None	No
Fazio et al[66], 2003	Cleveland, US	1983-2001	Yes	Prospective	Some	Yes

Fowler et al[67], 2003	Gloucester, UK	1984-2001	Yes	Prospective	Some	No
Michelassi et al[68], 2003	Chicago, US	1987-2002	Yes	Prospective	Some	Yes
Gosselink et al[69], 2004	Rotterdam, Netherlands	1989-2001	Yes	Prospective	Some	Yes
Hueting et al[70],2004	Utrecht, Netherlands	1989-2000	No	Retrospective	Some	No
Ikeuchi et al[71], 2004	Hyogo, Japan	1984-2002	No	Retrospective	All	No
Marciniak et al[72], 2004	Poznan, Poland	1984-2002	No	Retrospective	All	No
Pishori et al[73], 2004	Florida, US	1988-2000	Yes	Retrospective	Some	No
Arai et al[74], 2005	Yokohama, Japan	1993-2003	Yes	Retrospective	Some	No
Brown et al[75], 2005	Toronto, Canada	1982-2001	Yes	Prospective	Some	Yes
Hallberg et al[76], 2005	Stockholm, Sweden	1990-1997	No	Prospective	All	Yes
Ikeuchi et al[77], 2005	Hyogo, Japan	1999-2003	No	Retrospective	Some	No
Krausz et al[78], 2005	Haifa, Israel	1984-2004	Yes	Retrospective	Some	No
Araki et al[79], 2006	Paris, France	1998-2003	Yes	Prospective	None	No
Bengtsson et al[80], 2007	Goteborg, Sweden	1984-2004	No	Retrospective	All	No
Berndtsson et al[81], 2007	Goteborg, Sweden	1982-1995	No	Retrospective	All	No
Das et al[82], 2007	St Marks, UK	1978-2006	No	Retrospective	All	No
Hahnloser et al[83], 2007	Mayo Clinic, US	1981-2000	Yes	Prospective	Some	Yes
Nilubol et al[84], 2007	New York, US	1988-1999	No	Prospective	All	Yes
Abdelrazeq et al[85], 2008	York, UK	1988-2003	Yes	Retrospective	All	Yes
Ferrante et al[86], 2008	Leuven, Belgium	1990-2004	Yes	Retrospective	All	Yes
Fleshner et al[87], 2008	Los Angeles, US	NR	Yes	Prospective	All	No
Hoda et al[88], 2008	Oregon, US	1993-2003	No	Retrospective	All	No
Lovegrove[89], 2008	Sheffield, UK	1987-2006	No	Prospective	None	No
Tulchinsky et al[90], 2008	Tel-Aviv, Israel	1986-2005	No	Prospective	All	No
Rink et al[91], 2009	Guttenberg, Germany	1990-2002	Yes	Retrospective	Some	Yes

Table 4.2 Characteristics of Patients in IPAA Studies

Author	N	Patient Mean Age (Range) y	% Crohn's	% FAP	% IC	% Diversion	% Prior-subtotal	% Stapled	% J-pouch	Length of Follow-up	Loss to Follow-up (%)
Fonkalsrud et al[25],1988	172	23.8(7-58)	0	9.3	2.7	100	NR	44.8	87.5	NR	NR
Nicholls et al[26], 1989	116	30 (14-52)	0	0	0	75.8	62.5	0	12.9	41	1.3
Pescatori and Mattana[27], 1990	207	34 (8-67)	0	31.4	0	99.3	30	24.2	63.3	13.4	NR
Wexner et al[28], 1990	180	31	0	6.1	0	100	12.2	0	1.1	60	1.1
Becker et al[29], 1991	250	35 (11-67)	0	16	0	100	NR	100	100	NR	0
Harms et al[30], 1992	109	32.4 (11-67)	0	17.4	0	100	98.1	0	0	33.6	0
Fischer et al[31], 1993	200	NR	0	0	0	100	NR	0	3.5	NR	2.5
Mathey et al[32], 1993	157	33.5 (10-65)	0	19	0	100	56.7	12.1	82.8	37	26
Sagar et al[33], 1993	103	34 (14-64)	0	10.7	0	100	NR	66.9	13.6	NR	6.3
Atkinson et al[34], 1994	158	34 (19-59)	0	0	0	100	NR	100		NR	NR
Daude et al[35], 1994	156	35	0	0	0	100	35	0	100	29	0
Hulten et al[36],1994	307	NR	0	0	0	100	NR	NR	NR	66	17
Lewis et al[37], 1994	115	35	1.7	6.1	0	67.8	35.6	0	10.4	34	0
Gorfine et al[38], 1995	143	34	0.7	9.8	0.7	48.3	46.8	0	100	18	6.3
Hewett et al[39], 1995	126	NR	0	0	0	100	NR	0	51.4	51	15
Sitzmann et al[40], 1995	105	NR	0	17.1	8.5	100	29.5	0	100	37.2	0
Stahlberg et al[41], 1996	149	34*(8-64)	0	0	0	100	NR	100	100	54*	0
McCourtney and Finlay[42],1997	103	31 (12-77)	0	8.7	0	73.8	26.2	100	100	31	3.9
Romanos et al[43], 1997	200	33 (6-67)	0	3.5	6.5	69.5	NR	73.5	71	27*	2.0
Breen et al[44], 1998	628	NR	0.3	8.3	7.5	100	NR	NR	NR	56	3.7
Belliveau et al[45], 1999	239	34	4.1	4.6	0	100	36.8	32.8	32.8	NR	NR
Fazio et al[46], 1999	977	37	3.5	3.8	12.6	100	NR	100	80.1	60	15
Neilly et al[47], 1999	187	32 (14-63)	3.9	9.4	3.4	51.7	NR	74.1	65.2	73.2	7.9
Tiainen et al[48], 1999	136	35.5(19-63)	0	0	0	100	47.1	2.1	100	NR	NR
Young et al[49], 1999	100	35*(5-68)	0	20	5	100	42	50	100	68	0
Karlbom et al[50], 2000	182	32 (16-68)	0	0	0	70.8	56	45.8	45.8	29*	8
Keighley et al[51], 2000	202	35.6 (13-77)	0	0	0	100	57.4	90.6	90.6	91.3	0
Mowschenson et al[52],2000	133	34.1	0	2.3	0	30.8	NR	100	100	NR	16.5
Simchuk and Thirlby[53], 2000	114	39 (16-72)	2.6	11.4	0	100	NR	0	100	38	2.6

Sugerman et al[54], 2000	192	38 (7-70)	2.6	4.2	0.5	0	88.5	100	100	61.2	11
Blumberg et al[55], 2001	145	34 (14-70)	0	23.4	0	83.4	15.2	NR	35.9	NR	NR
Heuschen et al[56], 2001	210	34.4	0	0	0	100	NR	100	100	51	11.5
Madiba and Bartolo[57], 2001	139	38.2 (13-74)	0	0	0	100	25.2	0	97.1	60	NR
Regimbeau et al[58], 2001	172	36 (16-72)	24.4	27.9	0	100	NR	0	100	60	26
Dayton et al[59], 2002	565	37	0	0	0	100	14	100	100	78.5	11
Heuschen et al[60], 2002	494	34.2*	0	0	0	91	29.8	100	100	56.7*	3.2
Lepisto et al[61], 2002	486	NR	0	7.4	0	32.7	15	7.8	NR	NR	NR
MacLean et al[62], 2002	1178	40.7	0	5.6	0	66	50	NR	NR	104.4	8.1
Robb et al[63], 2002	379	35.9 (5-84)	1.6	10.3	0	100	NR	10.8	10.8	103.3	14.2
Rudolph et al[64], 2002	120	38 (7-72)	11.7	0	29.2	76.7	5.8	NR	NR	47	1.2
de Oca et al[65], 2003	100	32 (15-63)	0	0	1	100	78	NR	NR	83	NR
Fazio et al[66], 2003	1965	37.5	3.8	7.3	27.9	86.7	35.1	85.3	87.4	49.2	24.2
Fowler et al[67], 2003	106	40(13-77)	3.8	10.4	1.9	41.3	NR	0	0	NR	1
Michelassi et al[68], 2003	391	33.7 (12-66)	0	0	3.3	65	NR	29.9	100	24*	9.7
Gosselink et al[69], 2004	127	35* (14-67)	3.9	0	0	21.3	73.2	0	3.1	68*	0
Hueting et al[70],2004	111	35.4	0	0	0	NR	NR	NR	NR	42*	18.9
Ikeuchi et al[71], 2004	521	NR	0	0	0	NR	NR	5.7	100	NR	NR
Marciniak et al[72], 2004	110	NR	0	34.5	0	NR	NR	NR	NR	21.6	NR
Pishori et al[73], 2004	303	NR	1.6	0	4.3	97	36.3	100	100	40	NR
Arai et al[74], 2005	296	33.8	0	0	0	55.4	2.4	96.3	100	52.6	0
Brown et al[75], 2005	1135	34	0	0	0	64.7	57.2	71.2	81.6	98	0
Hallberg et al[76], 2005	100	32*(12-71)	0	0	0	71	NR	100	100	48*	10
Ikeuchi et al[77], 2005	242	33*(15-69)	0	0	0	38	NR	0	100	NR	NR
Krausz et al[78], 2005	174	NR	0	16.1	0	87.4	NR	46	63.2	64.8	24.7
Araki et al[79], 2006	123	37.5(10-69)	0	0	5.7	66.7	41.5	0	100	NR	0
Bengtsson et al[80], 2007	620	35.5 (13-75)	1.8	4.7	0	NR	NR	NR	NR	168	6.9
Berndtsson et al[81], 2007	399	34 (13-74)	0	0	0	NR	NR	NR	33.6	180*	7.3
Das et al[82], 2007	1822	NR	NR	NR	NR	NR	NR	NR	NR	120*	NR
Hahnloser et al[83], 2007	1885	34 (12-68)	0	0	0	98.4	NR	NR	96.8	129.6	0
Nilubol et al[84], 2007	138	36.1	1.4	7.2	5.8	100	NR	0	87.7	64.8	6.5
Abdelrazeq et al[85], 2008	198	38.3 (14-64)	0	0	0	68.2	NR	100	100	64	3
Ferrante et al[86], 2008	173	39	0	0	1.2	66.5	18.5	95.4	97.7	78	6

Fleshner et al[87], 2008	238	38 (8-81)	0	0	29.4	100	NR	NR	100	47	0
Hoda et al[88], 2008	167	36	0	0	0	91.5	34.7	NR	NR	NR	29.5
Lovegrove et al[92], 2008	199	37.6	0.5	5	8.5	20.1	43.5	99	99.5	NR	NR
Tulchinsky et al[90], 2008	120	37 (13-75)	0	0	0	86.7	21.6	NR	NR	65	16.1
Rink et al[91], 2009	131	33 (12-70)	0	0	0	84	23.7	0	100	85	3.1

4.2.4 Complications

Pouch Failure

Forty-six studies totaling 15,793 patients reported on pouch failure with individual study estimates ranging from 1.0% to 16.7%[25-28, 32, 34-45, 47, 49-55, 58, 59, 61, 64, 66-69, 73-76, 78, 80-83, 86, 89, 91, 93]. The pooled estimate including all studies was 5.5% (95% CI, 4.7%-6.5%) with significant heterogeneity p=<0.001 and I^2 at 77.3% (Table 4.3, page 111). Figure 4.1 graphically summarizes each study's estimate, 95% confidence interval, and the pooled estimate. Studies with ≥85% J-pouch and studies with ≥85% diverting ileostomy had lower rates of pouch failure when compared to the overall rate, 3.8% (95% CI, 2.9%-5.1%) and 4.6% (95% CI, 3.6%-5.9%) respectively (Table 4.4, page 111). Studies with at least 5 years of follow-up had higher rates of pouch failure at 6.3% (95% CI, 5.1%-7.7%) when compared to the overall rate. Restricting the analysis to studies with less than 10% loss to follow-up had little effect on the summary estimate (Table 4.4). Despite division into subgroups, heterogeneity remained significant for all groups. At the study level, only the length of follow-up was associated with a statistically significant increase in the rate of pouch failure in both univariable and multivariable meta-regression, accounting for 16.83% of between study heterogeneity (p = 0.05, Figure 4.2). Funnel plot of the outcome on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of pouch failure (Figure 4.3).
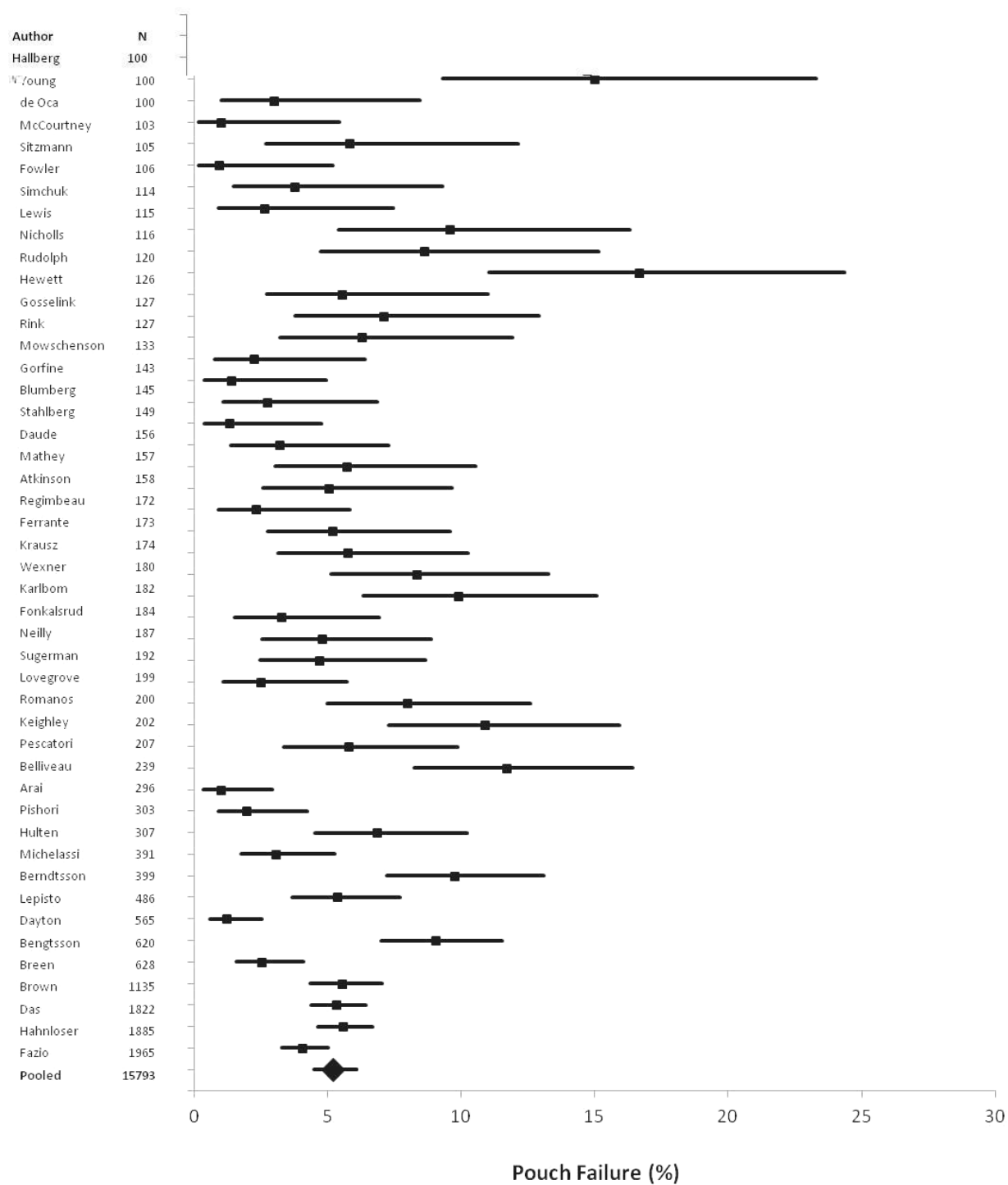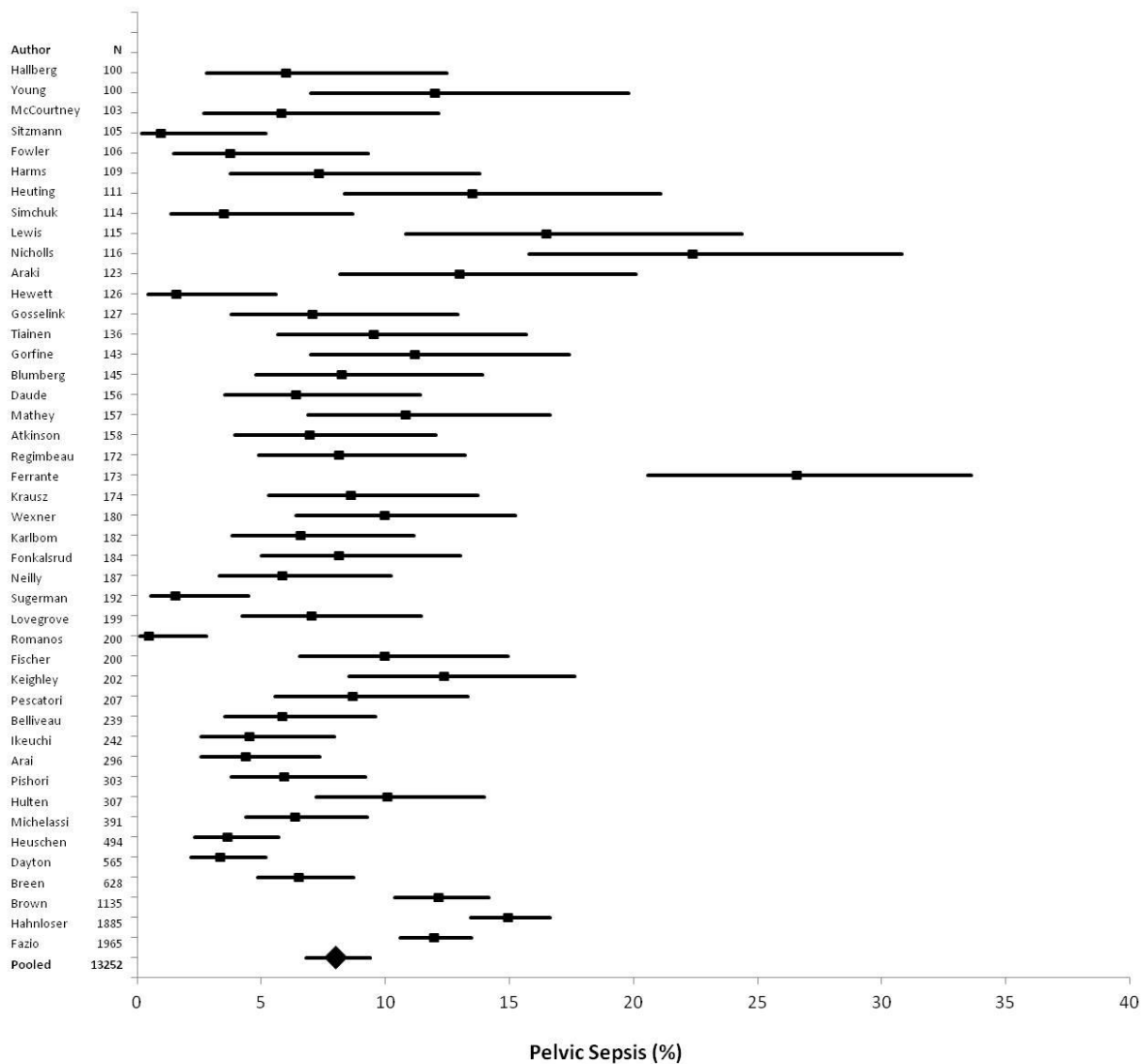
Figure 4.1 Forrest plot of studies reporting on rates of pouch failure. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
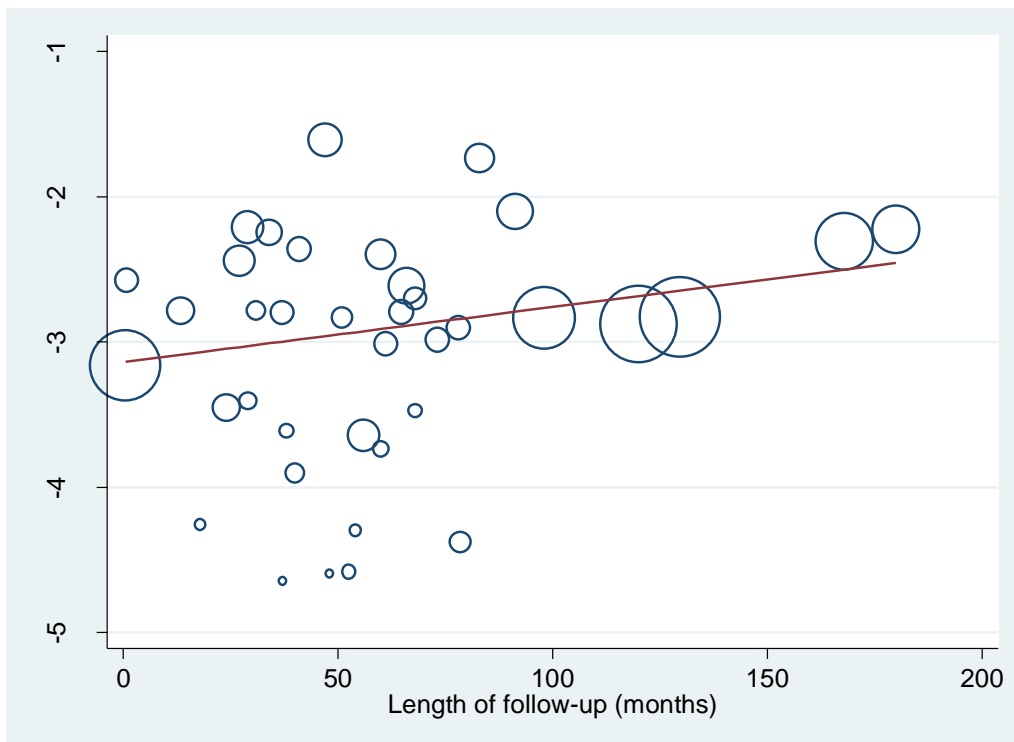
Figure 4.2 Meta-regression of length of follow-up on rate of pouch failure (ln(odds)). Studies with longer follow-up had higher rates of pouch failure, accounting for 16.6% of between-study variability ($p = 0.05$). The area of the circle is proportional to the number of patients in each study.
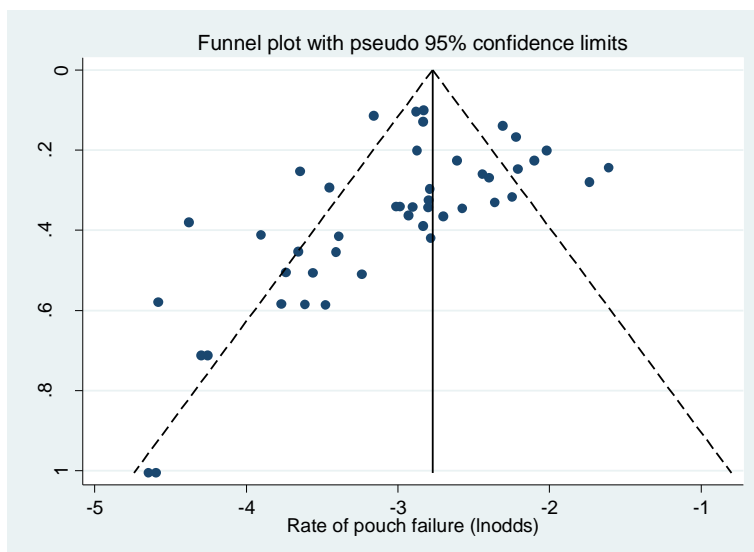
Figure 4.3 Funnel plot showing rate of pouch failure (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of pouch failure.

Pelvic Sepsis

Forty-four studies totaling 13,252 patients reported on pelvic sepsis with individual study estimates ranging from 0-26% [25-28, 30-32, 34-40, 42-45, 47-51, 53-55, 58-60, 66-70, 73-79, 83, 86, 89]. The pooled estimate including all studies was 8.0% (95% CI, 6.8%-9.4%) with significant heterogeneity p = <0.001 and I^2 at 84.8% (Table 4.3). Figure 4.4 graphically summarizes each study`s point estimate, its 95% confidence interval, and the pooled estimate. Studies with ≥85% use of diverting ileostomy had slightly lower rates of pelvic sepsis when compared to the overall rate 6.9% (95% CI, 5.7%-8.7%). While studies with > 5 years follow-up, and <10% lost to follow-up had slightly higher rates of pelvic sepsis, 9.1% (95% CI, 6.9-12.2) and 9.0% (95% CI, 7.2%-11.1%) respectively. Restricting the analysis to studies with ≥85% J-pouch had little effect on the summary estimate (Table 4.4). At the study level, only study type was associated with a change in rate of pelvic sepsis with a significant increase in the rate of pelvic sepsis among prospective studies in both univariable and multivariable meta-regression, accounting for 25.09% of between study variability (p = 0.005, Figure 4.5). Prospective studies (13 studies, n = 7,150) reported higher rates of pelvic sepsis when compared to the overall rate, 11.4% (95%CI, 9.3%-14.1%). Funnel plot of the outcome on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of pelvic sepsis (Figure 4.6).

Figure 4.4 Forrest plot of studies reporting on rates of pelvic sepsis. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
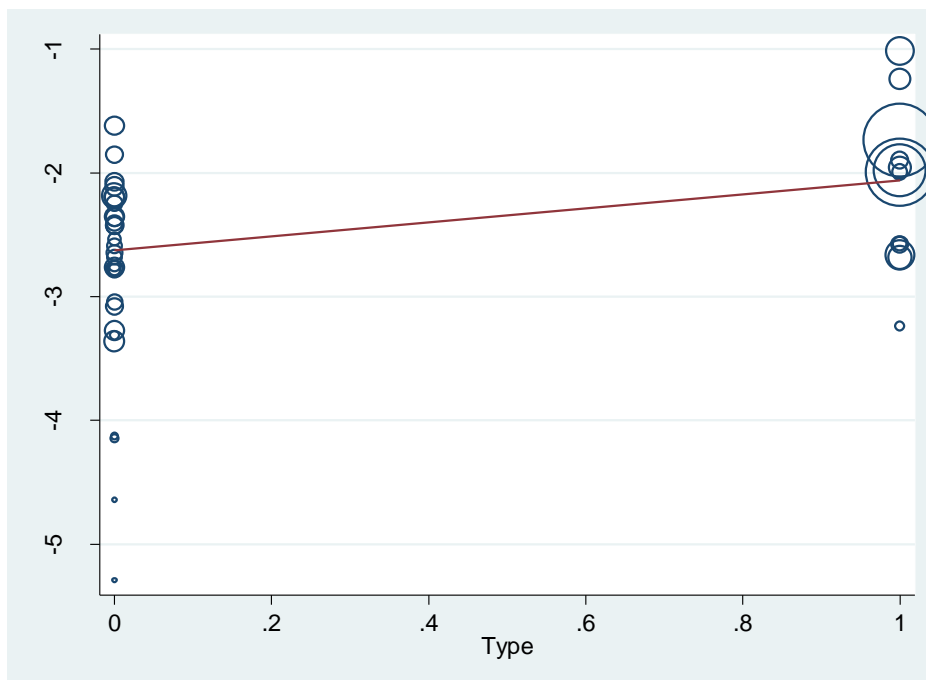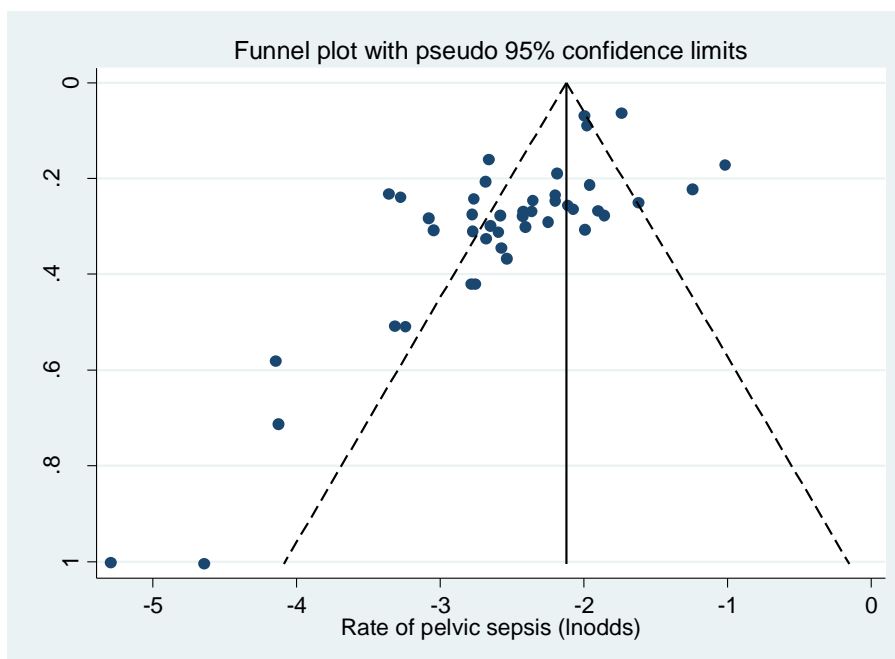
Figure 4.5 Meta-regression of study type (0 = retrospective, 1 = prospective) on rate of pelvic sepsis (ln(odds)). Prospective studies reported higher rates of pelvic sepsis, accounting for 25.09% of between study variability (p = 0.005). The area of the circle is proportional to the number of patients in each study.

Figure 4.6 Funnel plot showing rate of pelvic sepsis (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of pelvic sepsis.

Pouch Fistula

Thirty-six studies totaling 12,155 patients reported on pouch fistula with individual study estimates ranging from 1.6-15.8%[25, 26, 28, 32, 34-36, 39, 43-45, 47, 48, 51, 53-55, 58-61, 64, 66-70, 73-75, 77, 78, 83, 86, 89-91, 93]. The pooled estimate including all studies was 5.1% (95% CI, 4.1%-6.5%) with significant heterogeneity p = <0.001 and I^2 at 88.5% (Table 4.3). Figure 4.7 graphically summarizes each study`s point estimate, its 95% confidence interval, and the pooled estimate. Studies with at least 5 years of follow-up had higher rates of pouch fistula at 6.5% (95% CI, 3.7%-8.9%). Restricting the analysis to studies with ≥85% J-pouch, ≥85% diverting ileostomy, or < 10% follow-up had little effect on the summary estimate (Table 4.4). At the study level, only outcome criteria definition was associated with a change in rate of pouch fistula. In both univariable and multivariable meta-regression, studies using clearly defined outcome criteria reported higher rates of pouch fistula, accounting for 24.8% of between study variability (p = 0.003, Figure 4.8). Studies (9, n =2,264) using clearly defined outcome criteria reported higher rates of pouch fistula compared to the overall estimate 9.4% (95% CI,7.2%-12.3%). Funnel plot of the outcome on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of pouch fistula (Figure 4.9).
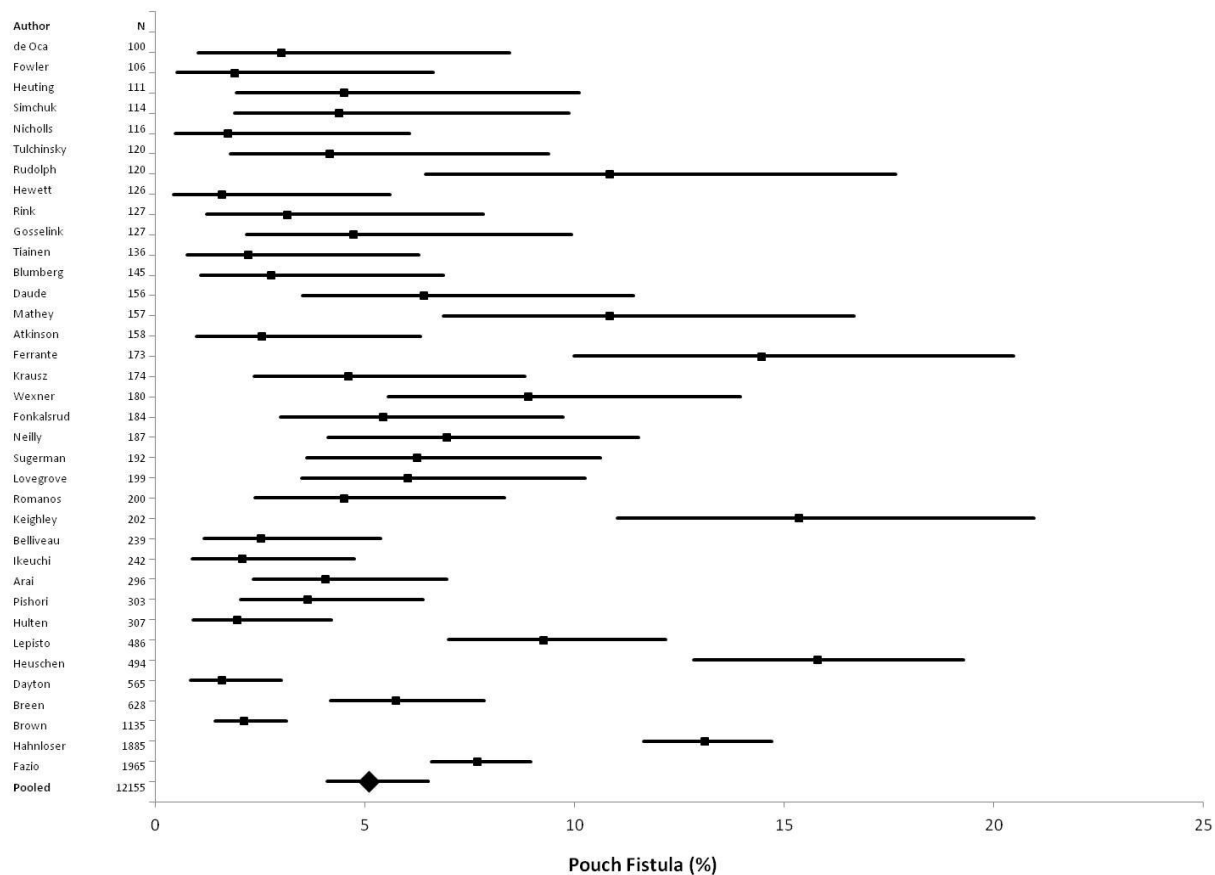
Figure 4.7 Forrest plot of studies reporting on rates of pouch fistula. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
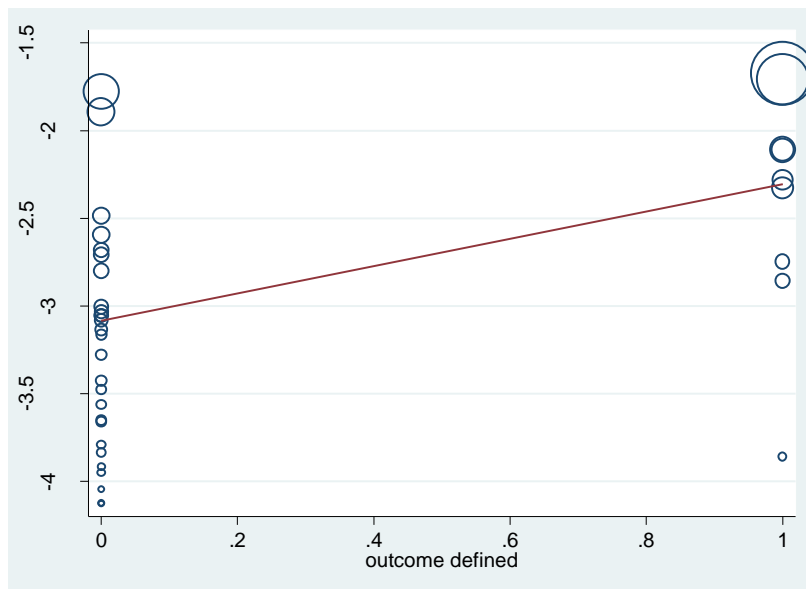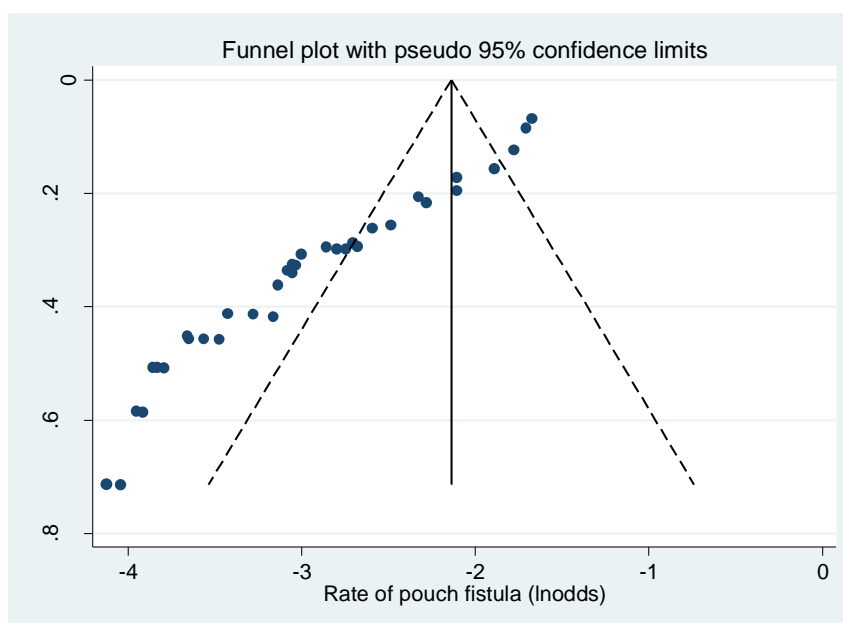
Figure 4.8 Meta-regression of outcome definition (0 = not defined, 1 = clearly defined) on rate of pouch fistula (ln(odds)). Studies with clearly defined outcomes reported higher rates of pouch fistula, accounting for 29.1% of between study variability (p = 0.003). The area of the circle is proportional to the number of patients in each study.

Figure 4.9 Funnel plot showing rate of pouch fistula (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of pouch fistula.

Anastomotic Stricture

Twenty nine studies totaling 7,533 patients reported on anastomotic stricture with individual study estimates ranging from 1.6-33%[25, 30, 32, 35-37, 40, 42-45, 47, 49-51, 53, 58, 59, 64, 66-69, 73, 76, 78, 79, 89, 93]. The pooled estimate including all studies was 9.1% (95% CI, 6.6%-11.5%) with significant heterogeneity p = <0.001 and I^2 at 89.7% (Table 4.3). Figure 4.10 graphically summarizes each study`s point estimate, its 95% confidence interval, and the pooled estimate. Restricting the analysis to studies with ≥85% J-pouch, ≥85% diverting ileostomy, at least 5 years of follow-up, or < 10% follow-up had little effect on the rate of anastomotic stricture (Table 4.4). At the study level, only outcome criteria definition was associated with a change in rate of anastomotic stricture. In both univariable and multivariable meta-regression, studies using clearly defined outcome criteria reported higher rates of anastomotic stricture, accounting for 19.4% of between study variability (p = 0.014, Figure 4.11). Studies (13, n =2,568) using clearly defined outcome criteria reported higher rates of pouch fistula compared to the overall estimate 12.6% (95% CI, 9.5%-16.7%). Funnel plot of the outcome on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of anastomotic stricture (Figure 4.12).
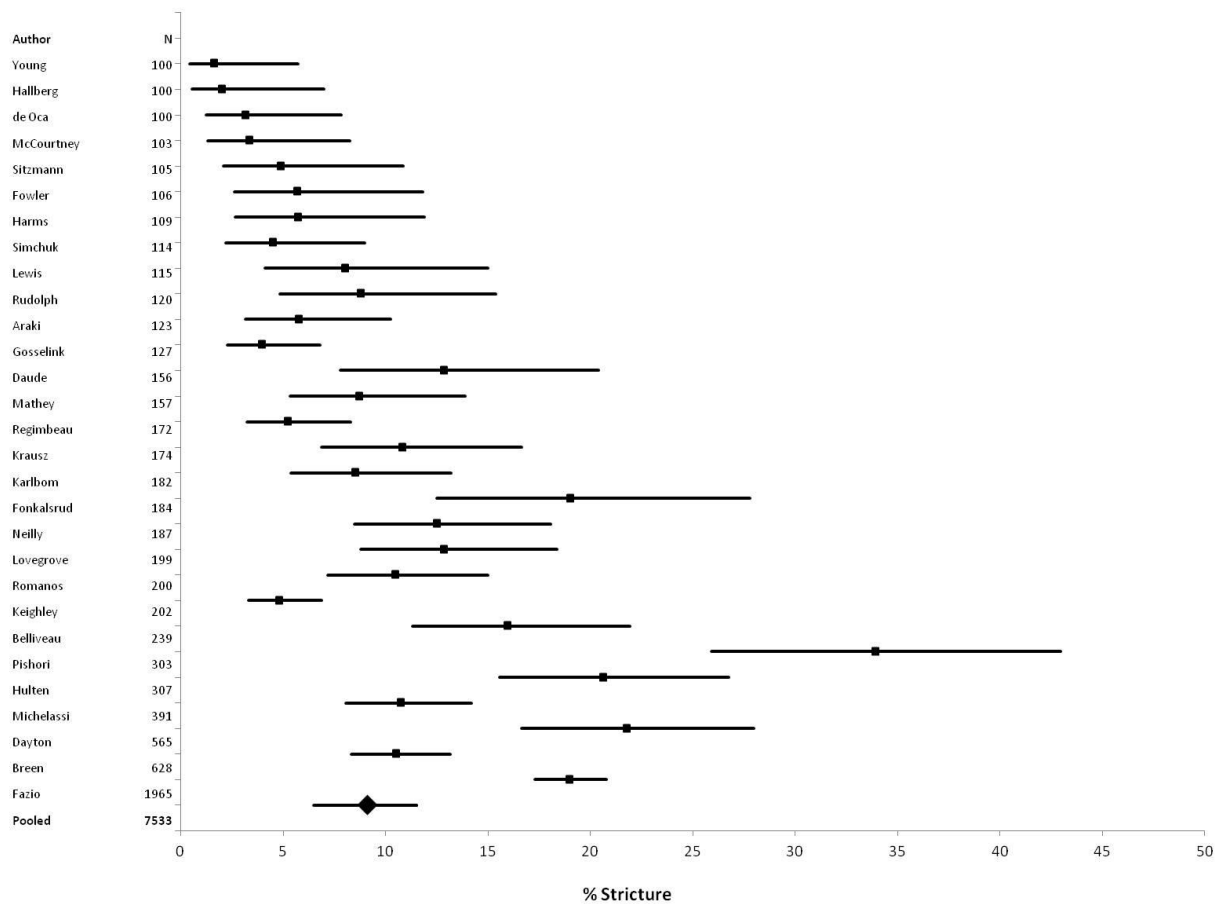
Figure 4.10 Forrest plot of studies reporting on rates of anastomotic stricture. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
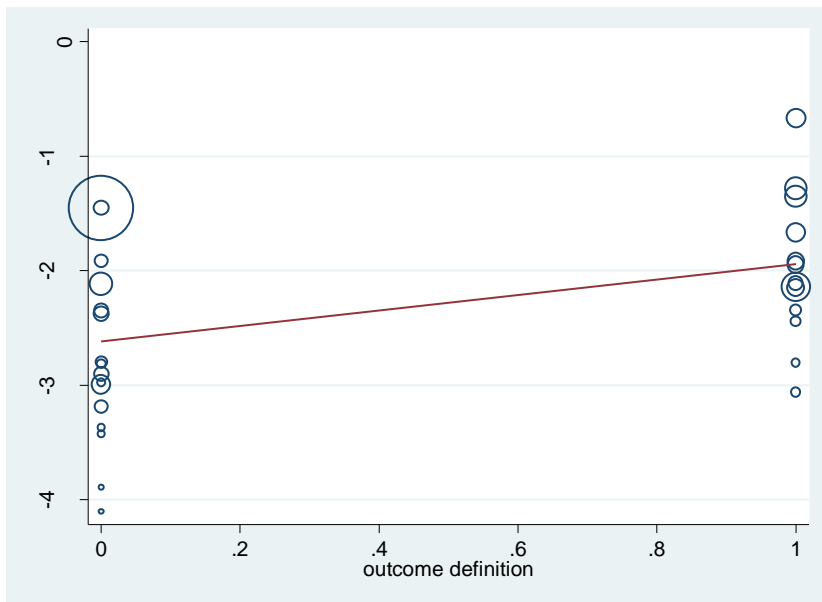
Figure 4.11 Meta-regression of outcome definition (0 =not defined, 1 = clearly defined) on rate of anastomotic stricture (ln(odds)). Studies with clearly defined outcomes reported higher rates of stricture, accounting for 19.4% of between study variability (p = 0.014). The area of the circle is proportional to the number of patients in each study.
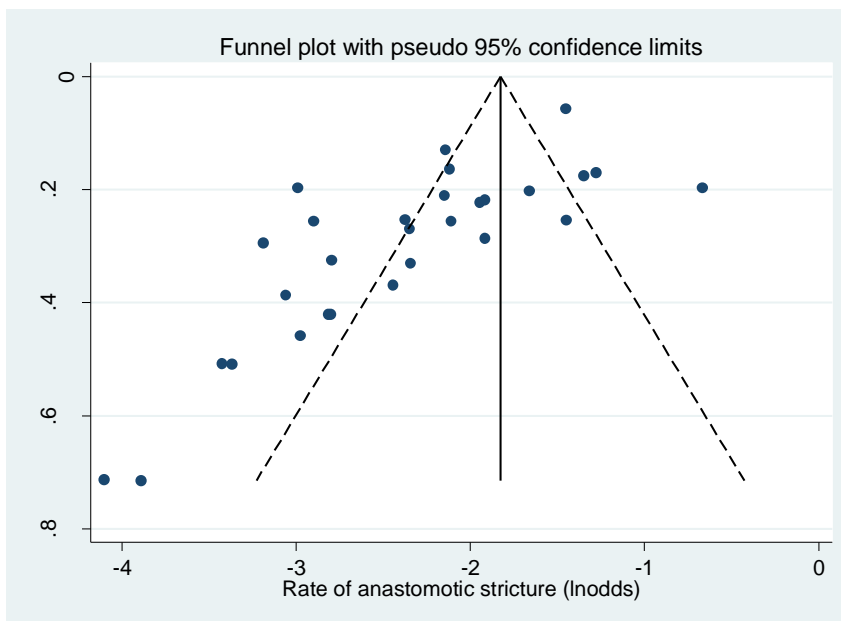

Figure 4.12 Funnel plot showing rate of anastomotic stricture (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of stricture.

Pouchitis

Fifty studies totaling 13,003 patients reported on rates of pouchitis with individual study estimates ranging from 2-60% [25, 27, 28, 30-32, 35-37, 39-43, 45, 47-59, 61, 63, 64, 66, 67, 69-74, 78, 83-86, 88-91, 93, 94]. The pooled estimate including all studies was 22.0% (95% CI, 19.4%-26.5%) with significant heterogeneity p = <0.001 and I^2 at 95.3% (Table 4.3). Figure 4.13 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with at least 5 years of follow-up had higher rates of pouchitis at 28.1% (95% CI, 22.3-34.6%). Restricting the analysis to studies with ≥85% J-pouch, ≥85% diverting ileostomy, or < 10% follow-up had little effect on the summary estimate (Table 4.4). At the study level, both outcome criteria definition and length of follow-up were associated with a change in the rate of pouchitis. In both univariable and multivariable meta-regression, studies using clearly defined outcome criteria reported higher rates of pouchitis, accounting for 17.22% of between study variability (p = 0.002, Figure 4.14), while the association with length of follow-up was only seen in univariable analysis. Studies (26, n =8,360) using clearly defined outcome criteria reported higher rates of pouchitis compared to the overall estimate, 28.7% (95% CI, 23.6%-34.5%). Funnel plot of the outcome on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of pouchitis (Figure 4.15).
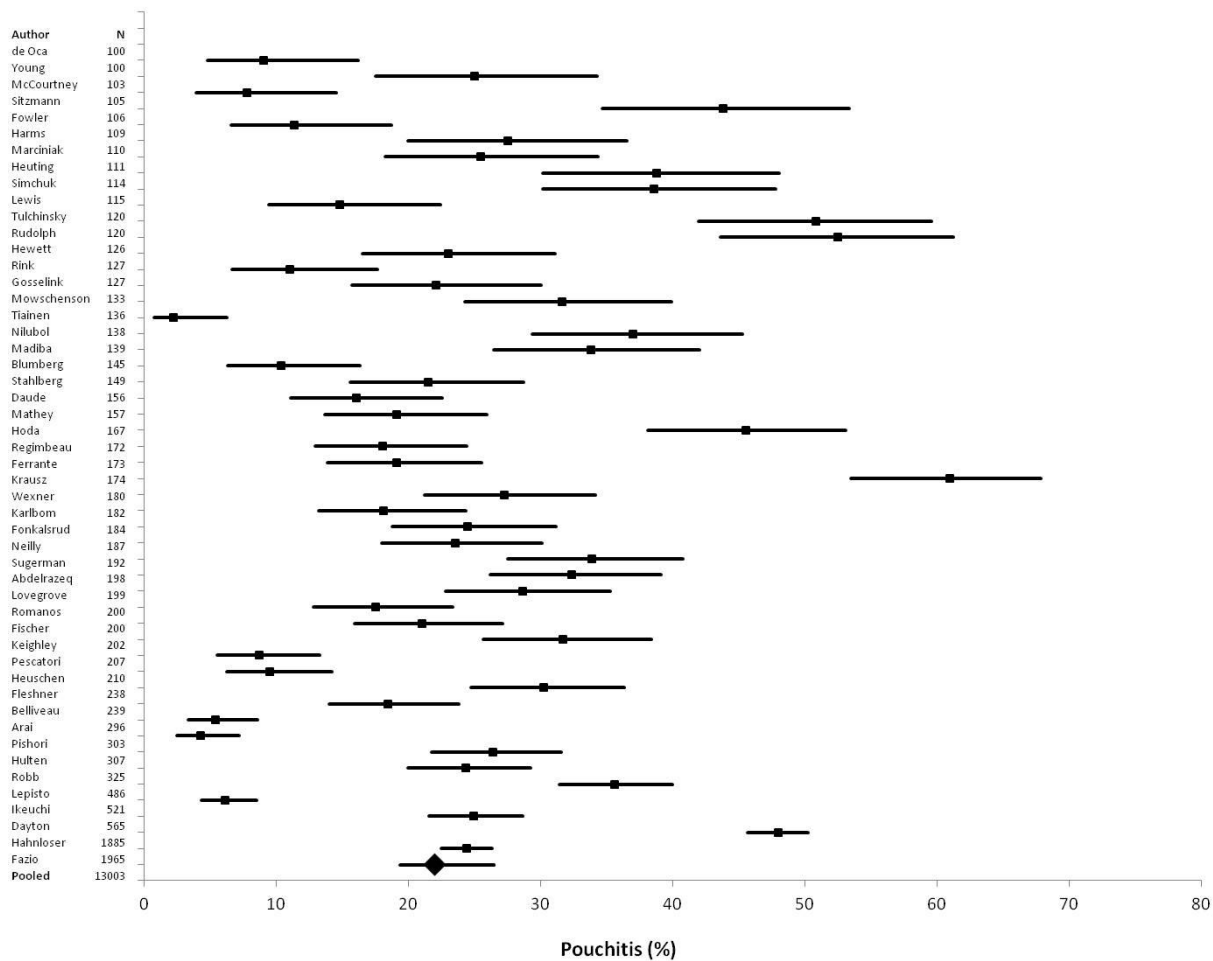
Figure 4.13 Forrest plot of studies reporting on rates of pouchitis. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
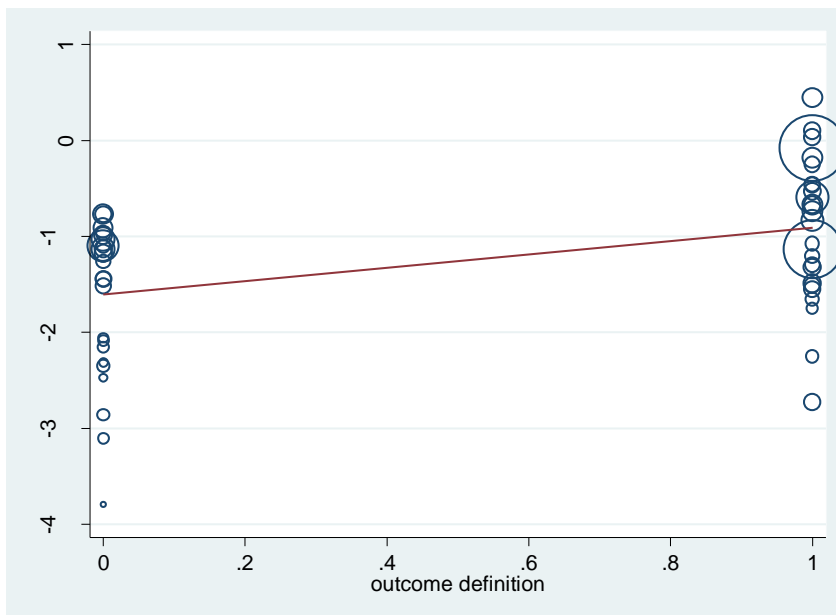
Figure 4.14 Meta-regression of outcome definition (0 =not defined, 1 = clearly defined) on rate of pouchitis (ln(odds)). Studies with clearly defined outcomes reported higher rates of pouchitis, accounting for 17.22% of between study variability (p = 0.002). The area of the circle is proportional to the number of patients in each study.
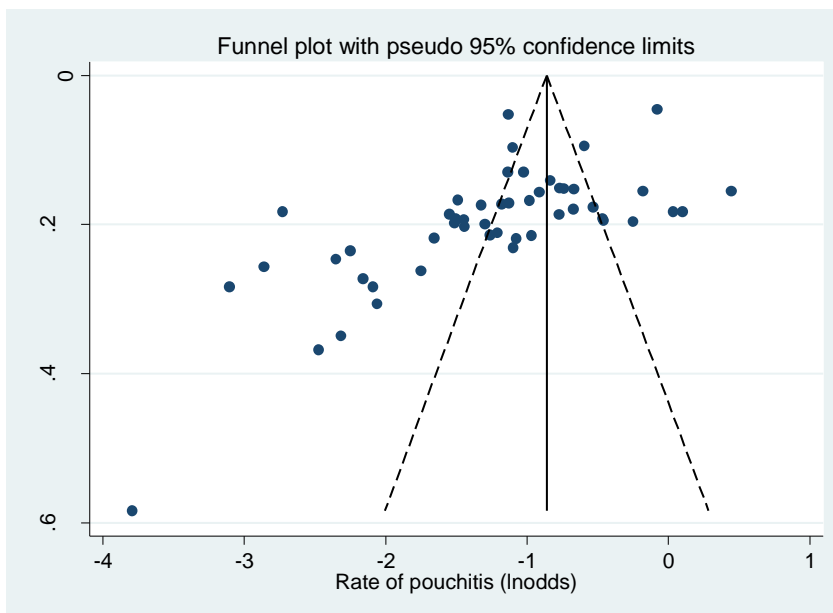

Figure 4.15 Funnel plot showing rate of pouchitis (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of pouchitis.

Small Bowel Obstruction

Thirty-five studies totaling 11,069 patients reported on the rates of small bowel obstruction (SBO), with individual study estimates ranging between 1% and 52%[25, 26, 28, 30-32, 36, 38-40, 43, 45, 47-49, 52-55, 58, 59, 62, 64, 66-69, 73, 74, 77, 78, 83, 86, 89, 93]. The pooled estimate including all studies was 11.8% (95% CI, 9.0%-15.3%) with significant heterogeneity p = <0.001 and I^2 at 96.6% (Table 4.3). Figure 4.16 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with at least 5 years of follow-up, and studies with less than 10% loss to follow-up had higher rates of small bowel obstruction at 13.2% (95% CI, 8.3%-20.1%) and 14% (95%CI, 9.8%-19.5%) respectively. Restricting the analysis to studies with ≥85% J-pouch, or ≥85% diverting ileostomy had little effect on the summary estimate (Table 4.4). In both univariable and multivariable meta-regression, studies using clearly defined outcome criteria reported higher rates of small bowel obstruction, accounting for 10.4% of between study variability (p = 0.04, Figure 4.17). Studies (5, n =1,054) using clearly defined outcome criteria reported higher rates of small bowel obstruction compared to the overall estimate, 22.5% (95% CI, 19.3%-26.5%). Funnel plot of the rate of small bowel obstruction on the log scale plotted against study size reveals evidence of publication bias with fewer small studies being published with higher rates of small bowel obstruction (Figure 4.18).
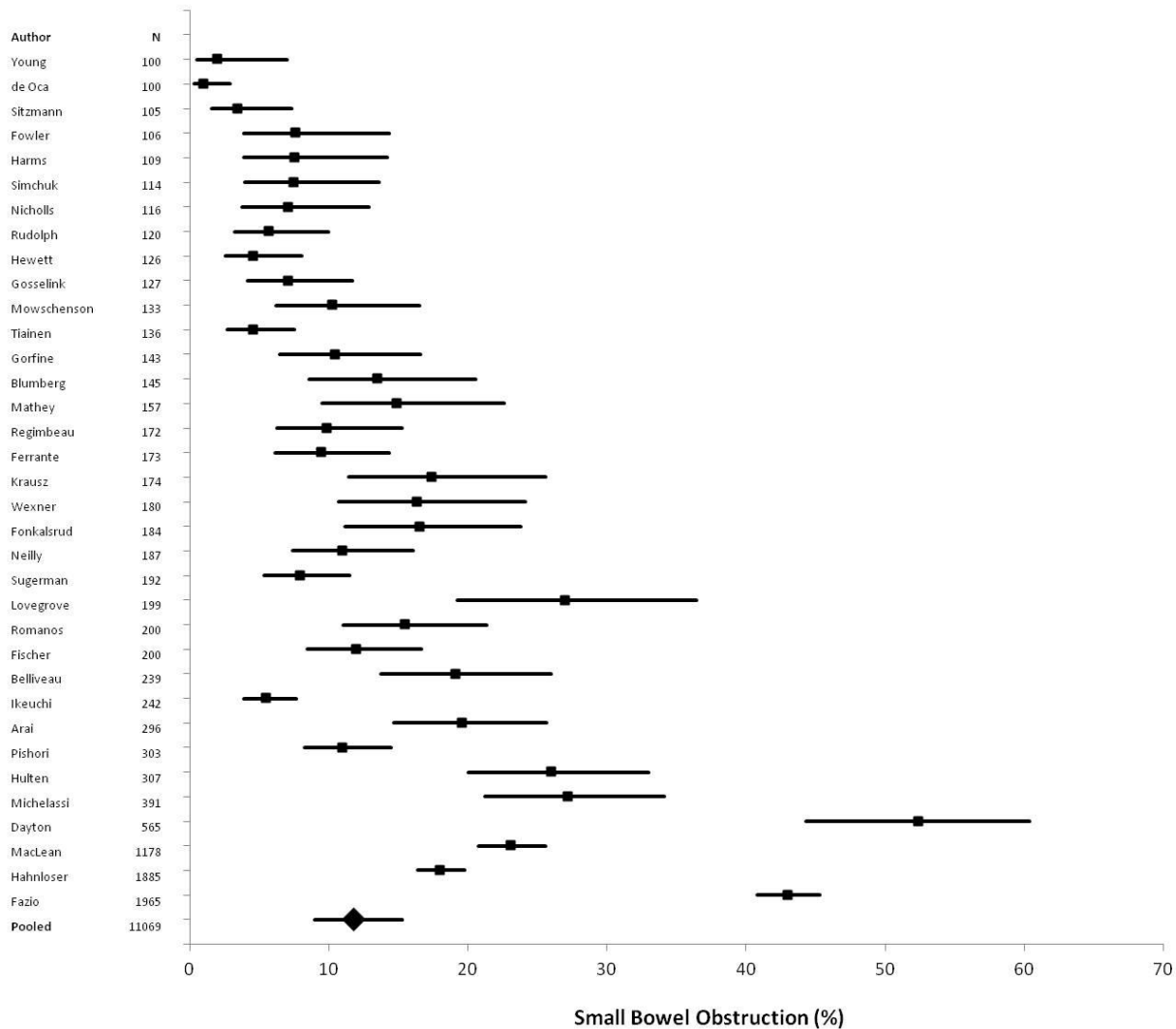
Figure 4.16 Forrest plot of studies reporting on rates of small bowel obstruction. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
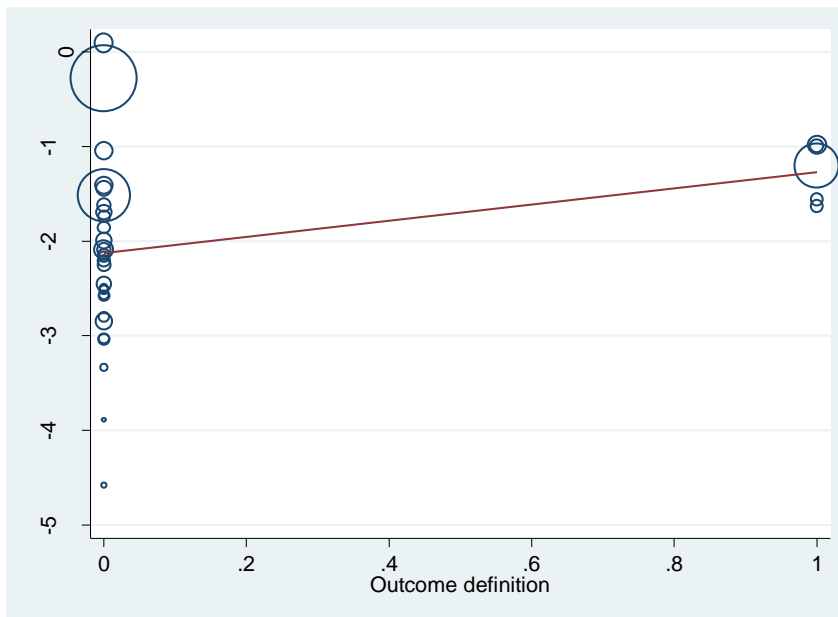
Figure 4.17 Meta-regression of outcome definition (0 =not defined, 1 = clearly defined) on rate of small bowel obstruction (ln(odds)). Studies with clearly defined outcomes reported higher rates of small bowel obstruction, accounting for 10.40% of between study variability (p = 0.041). The area of the circle is proportional to the number of patients in each study.

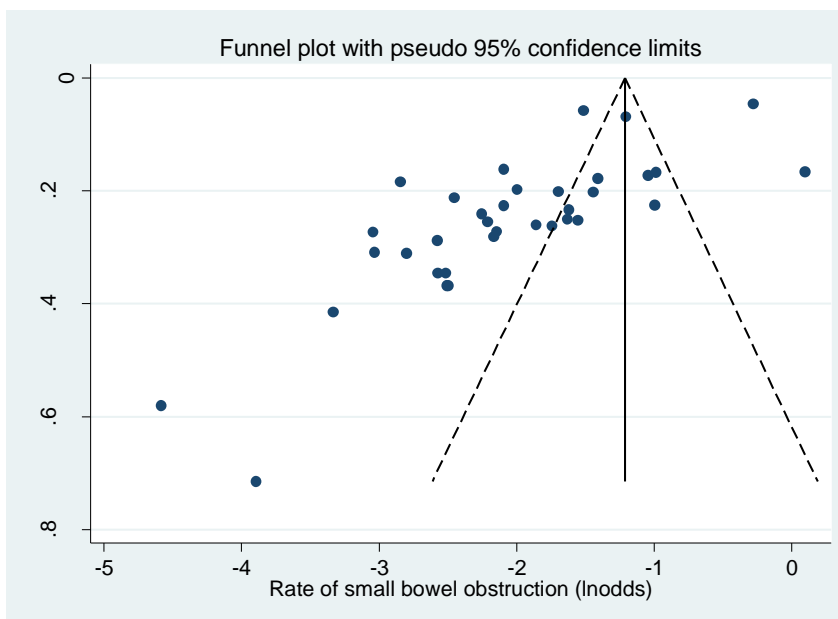
Figure 4.18 Funnel plot showing rate of small bowel obstruction (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of small bowel obstruction.

Sexual Dysfunction

Nineteen studies totaling 5,003 patients reported on the rates of sexual dysfunction, with individual study estimates ranging between 0% and 13.6% [25-27, 29, 31, 33, 35, 36, 39, 43, 47, 52, 54, 58, 78, 83, 89, 93]. The pooled estimate including all studies was 4.6% (95% CI, 3.0%-6.8%) with significant heterogeneity p = <0.001 and I^2 at 95.1% (Table 4.3). Figure 4.19 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with at least 5 years of follow-up had higher rates of sexual dysfunction at 5.9% (95% CI, 3.5%-9.8%), while studies with ≥85% J-pouch had lower rates of sexual dysfunction when compared to the overall rate, 3.1% (95% CI, 1,2%-9.7%). Restricting the analysis to studies with ≥85% diverting ileostomy or loss to follow-up of <10% had little effect on the summary estimate (Table 4.4). Meta-regression did not reveal any association between study level factors and rate of sexual dysfunction. Funnel plot of the rate of sexual dysfunction on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of sexual dysfunction (Figure 4.20).
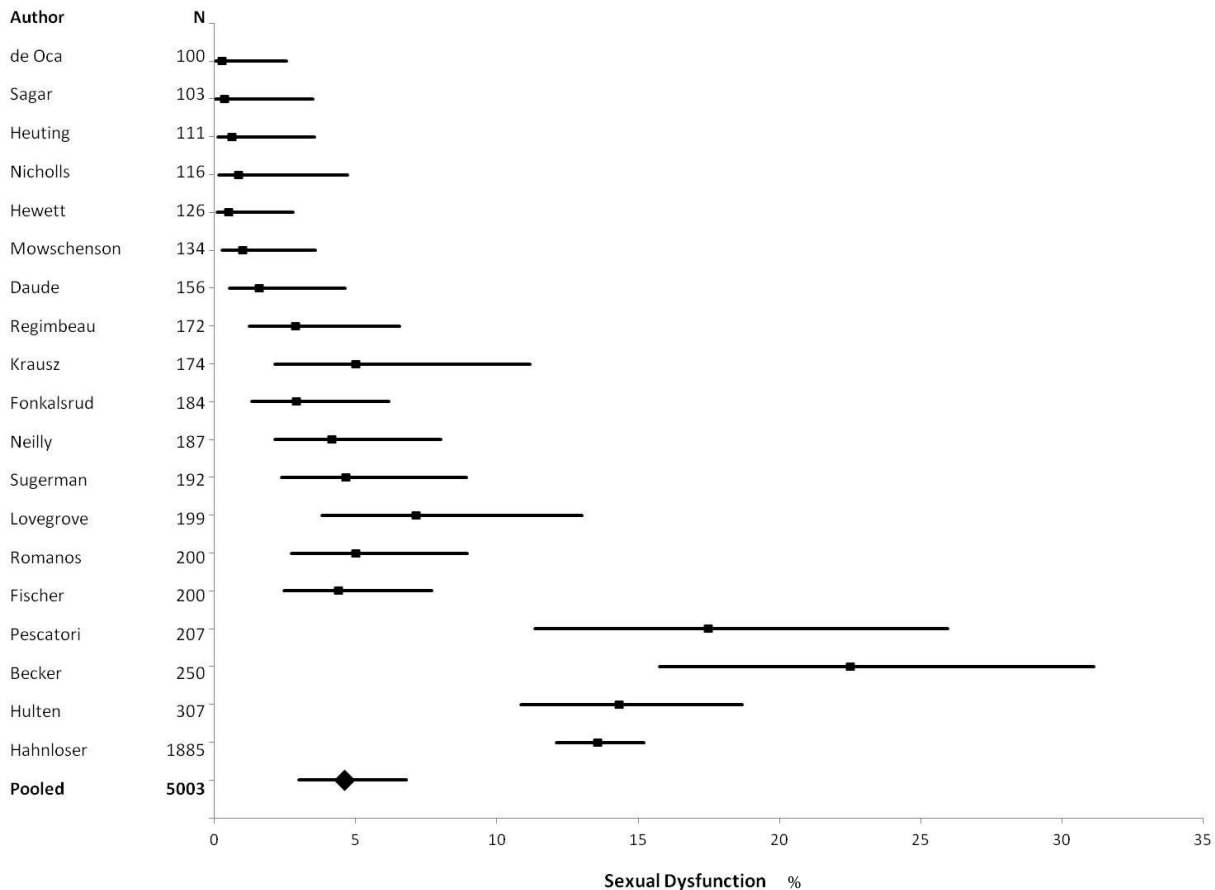
Figure 4.19 Forrest plot of studies reporting on rates of sexual dysfunction. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
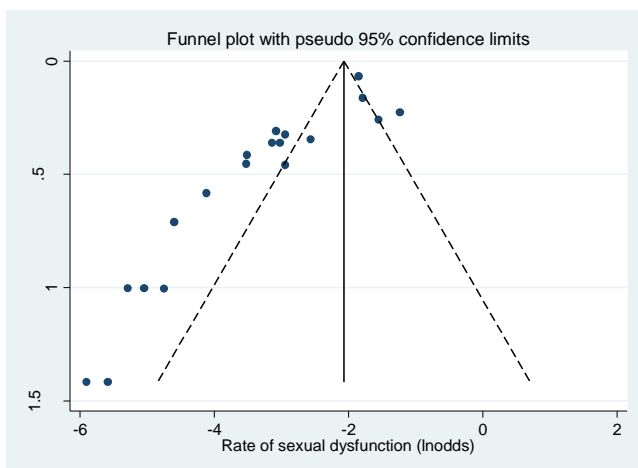

Figure 4.20 Funnel plot showing rate of sexual dysfunction (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of sexual dysfunction.

Table 4.3 Results of Meta-Analysis of Complication Rates Following IPAA

Complication	Number of Studies	Number of Patients	Pooled %	95% CI	I^2(%)	p
Pouch Failure	46	15,793	5.5	4.7-6.5	77.3	<0.001
Pelvic Sepsis	44	13,252	8.0	6.8-9.4	84.8	<0.001
Pouch fistula	36	12,155	5.1	4.1-6.5	88.5	<0.001
Stricture	29	7,533	9.1	6.5-11.5	89.7	<0.001
Pouchitis	50	13,003	22.0	19.4-26.5	95.3	<0.01
SBO	35	11,069	11.8	9.0-15.3	96.6	<0.001
Sexual dysfunction	19	5,003	4.6	3.0-6.8	95.1	<0.001

SBO small bowel obstruction

Table 4.4 Subgroup Meta-Analysis of Complications Following IPAA

Sub-Group	No. Studies	No. of Patients	Pooled %	95% CI	I^2	p
≥85% J-pouch						
Pouch failure	14	6,535	3.8	2.9-5.1	73.2	<0.001
Pelvic sepsis	16	7,425	7.5	5.6-9.9	91.7	<0.001
Pouch fistula	13	6,815	4.5	3.5-5.8	73.6	<0.001
Anastomotic stricture	10	4,194	9.1	6.1-13.8	93.4	<0.001
Pouchitis	18	7,954	21.3	16.2-27.4	92.5	<0.001
SBO	13	6,651	12.0	7.3-18.9	98.2	<0.001
Sexual dysfunction	5	2,581	3.1	1.2-9.7	89.8	<0.001
≥85% Diverting ileostomy				115		
Pouch failure	22	8,350	4.6	3.6-5.9	80.8	<0.001
Pelvic sepsis	24	8,985	6.9	5.7-8.7	86.5	<0.001
Pouch fistula	20	8,073	4.4	3.0-6.4	83.3	<0.001
Anastomotic stricture	17	5,581	8.9	6.6-11.9	91.0	<0.001
Pouchitis	30	9,168	24.2	20.0-29.0	95.8	<0.001
SBO	19	7,037	11.3	7.5-16.8	97.5	<0.001
Sexual dysfunction	12	3,864	5.3	3.4-8.3	87.9	<0.001
Follow-up ≥ 5yrs						
Pouch failure	17	8,290	6.3	5.1-7.7	76.8	<0.001
Pelvic sepsis	12	5,377	9.1	6.9-12.2	89.5	<0.001
Pouch fistula	13	5,338	6.5	3.7-8.9	92.7	<0.001
Anastomotic stricture	20	5,659	9.5	7.3-12.4	89.4	<0.001
Pouchitis	18	5,349	28.1	22.3-34.6	93.3	<0.001
SBO	13	5,123	13.2	8.3-20.1	97.4	<0.001
Sexual dysfunction	7	3,017	5.9	3.5-9.8	88.7	<0.001
< 10% lost to follow-up						
Pouch failure	26	8,049	5.7	4.6-7.1	79.4	<0.001
Pelvic sepsis	23	7,299	9.0	7.2-11.1	86.0	<0.001
Pouch fistula	17	6,449	5.8	4.0-8.3	88.5	<0.001
Anastomotic stricture	17	3,128	9.4	6.8-12.7	89.7	<0.001
Pouchitis	24	5,543	22.4	17.4-28.2	95.3	<0.001
SBO	18	5,663	14.0	9.8-19.5	96.4	<0.001
Sexual dysfunction	8	3,097	4.0	2.3-8.0	90.3	<0.001

4.2.5 Functional Results

Fecal Incontinence

Thirty studies totaling 9,284 patients reported on the rates of fecal incontinence, with individual study estimates ranging between 3% and 45%[26-32, 35, 38-40, 43, 44, 46, 47, 50, 52, 54, 64, 68-70, 74-76, 81, 83, 86, 89, 93]. The pooled estimate including all studies was 13.2% (95% CI, 9.9%-17.3%) with significant heterogeneity p = <0.001 and I^2 at 96.0% (Table 4.5). Figure 4.21 graphically summarizes each study's estimate, its 95% confidence interval, and the pooled estimate. Studies with at least 5 years of follow-up had higher rates of fecal incontinence at 15.9% (95% CI, 9.6%-25.4%), while studies with ≥85% J-pouch had lower rates, 9.1% (95%CI, 3.3%-24.5%). Restricting the analysis to studies ≥85% diverting ileostomy, or <10% follow-up had little effect on the summary estimate (Table 4.6). At the study level, outcome criteria definition (p = 0.009, Figure 4.22) and length of follow-up (p = 0.009, Figure 4.23) were associated with an increased rate of fecal incontinence, accounting for 22.59% and 19.91% of between study variability; while proportion of J-pouch (p = 0.009, Figure 4.24) was associated with a decrease rate of fecal incontinence, accounting for 22.06% of variability. These associations were seen at the univariable level, but lost their significance when subjected to multivariable meta-regression. Studies (9, n =4,354) using clearly defined outcome criteria reported higher rates of fecal incontinence compared to the overall estimate, 21.3% (95% CI, 13.6%-31.8%). Funnel plot of the rate of fecal incontinence on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of fecal incontinence (Figure 4.25).
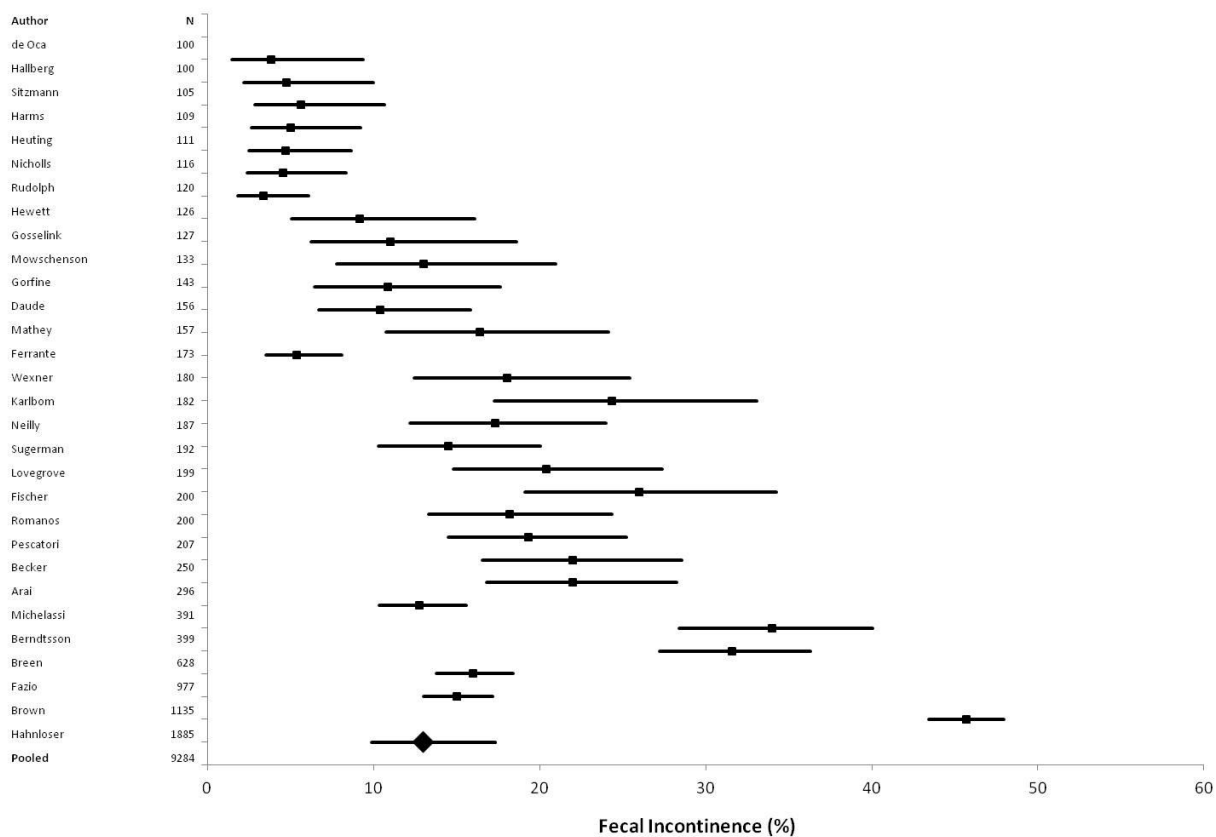
Figure 4.21 Forrest plot of studies reporting on rates of fecal incontinence. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
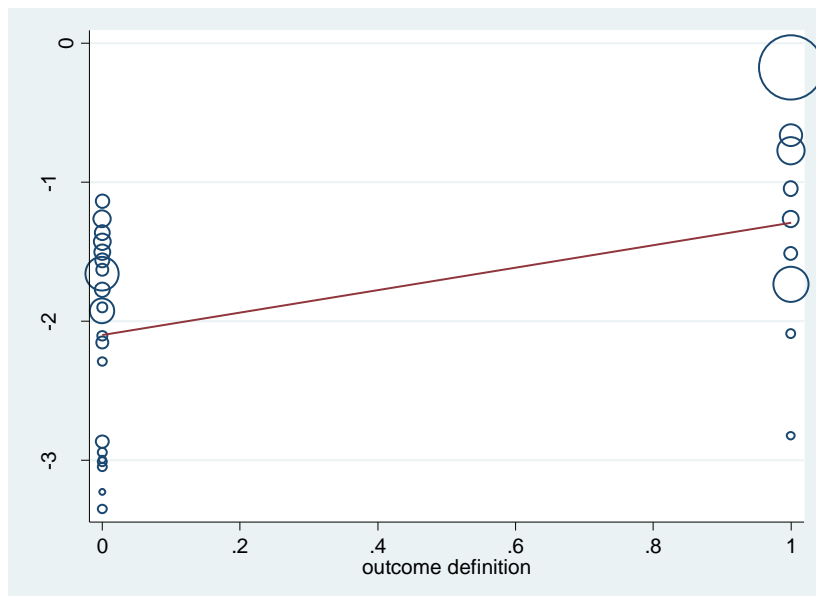
Figure 4.22 Meta-regression of outcome definition (0 =not defined, 1 = clearly defined) on rate of fecal incontinence (ln(odds)). Studies with clearly defined outcomes reported higher rates of fecal incontinence, accounting for 22.59% of between study variability (p = 0.009). The area of the circle is proportional to the number of patients in each study.
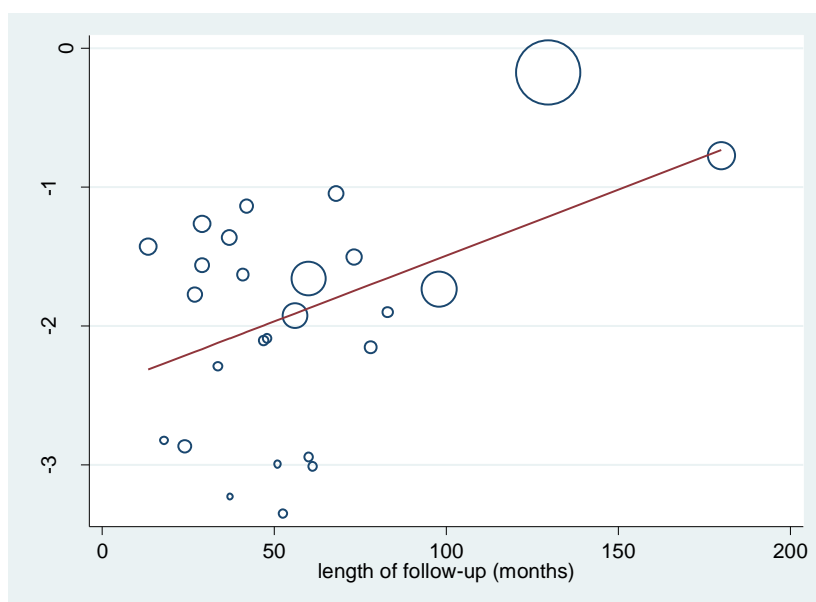

Figure 4.23 Meta-regression of length of follow-up (months) on rate of fecal incontinence (ln(odds)). Studies with longer follow-up reported higher rates of fecal incontinence, accounting for 19.91% of between study variability (p = 0.02). The area of the circle is proportional to the number of patients in each study

Figure 4.24 Meta-regression of proportion of patients with J-pouch on rate of fecal incontinence (ln(odds)). Studies with a higher proportion of J-pouch reported lower rates of fecal incontinence, accounting for 22.06% of between study variability (p = 0.04). The area of the circle is proportional to the number of patients in each study.

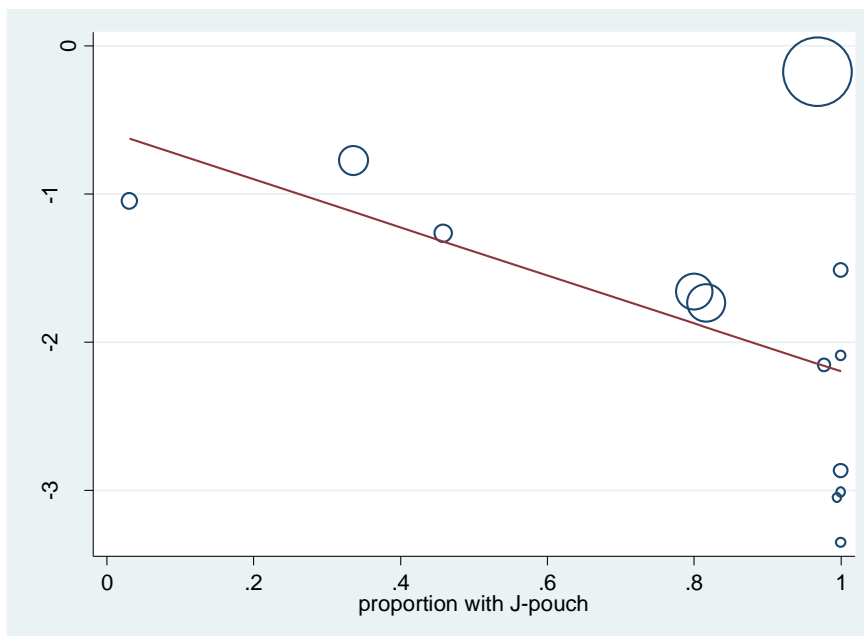
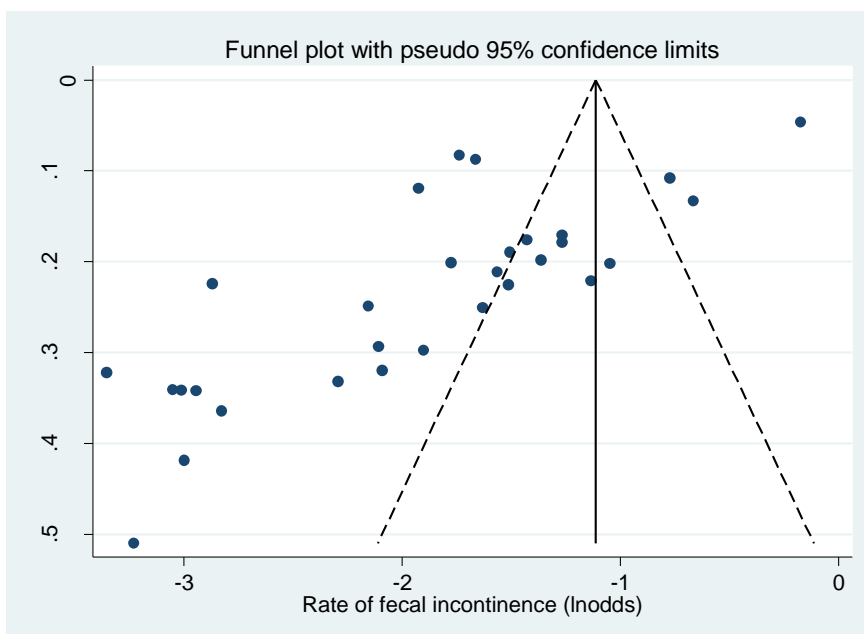
Figure 4.25 Funnel plot showing rate of fecal incontinence (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of fecal incontinence.

Fecal Urgency

Fourteen studies totaling 3,434 patients reported on the rates of fecal urgency, with individual study estimates ranging between 2.5-25%[32, 33, 35, 43, 47, 50, 52, 58, 70, 75, 81, 86, 89, 91]. The pooled estimate including all studies was 8.8% (95% CI, 6.4%-12.2%) with significant heterogeneity p = <0.001 and I^2 at 88.2% (Table 4.5). Figure 4.26 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with <10% loss to follow-up had higher rates of fecal urgency at 11.5% (95% CI, 6.4%-12.2%), while studies with ≥85% J-pouch had lower rates, 3.9% (95%CI, 2.4%-6.4%). Restricting the analysis to studies ≥85% diverting ileostomy, or at least 5 years of follow-up had little effect on the summary estimate (Table 4.6). At the study level, proportion of J-pouch was associated with a decrease rate of urgency, accounting for 74.65%% of between study variability (p = 0.008, Figure 4.27). Funnel plot of the rate of urgency on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of urgency (Figure 4.28).

Figure 4.26 Forrest plot of studies reporting on rates of fecal urgency. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.

Figure 4.27 Meta-regression of proportion of patients with J-pouch on rate of fecal urgency (ln(odds)). Studies with a higher proportion of J-pouch reported lower rates of fecal urgency, accounting for 74.65% of between study variability (p = 0.008). The area of the circle is proportional to the number of patients in each study.
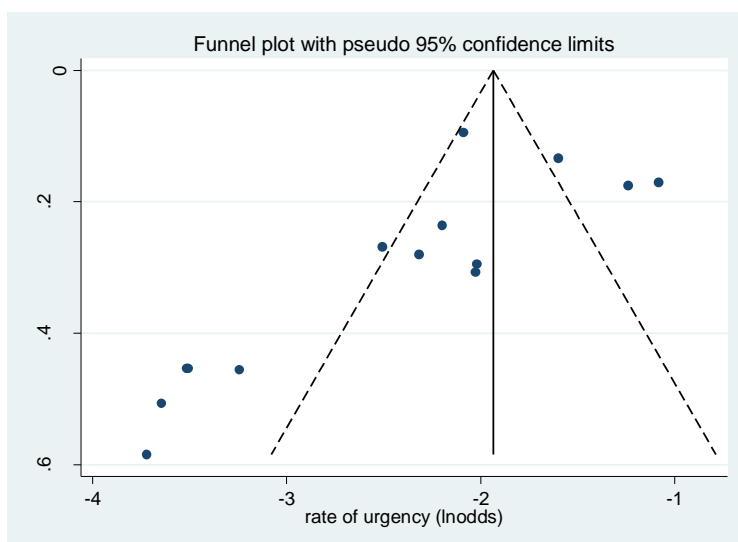
Figure 4.28 Funnel plot showing rate of fecal urgency (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of fecal urgency.

Pad Use

Twenty studies totaling 7,341 patients reported on the rates of pad use, with individual study estimates ranging between 2.1%-39%[28, 31-33, 37, 39, 44, 46, 50, 52, 54, 58, 70, 75, 78, 81, 83, 86, 89, 93]. The pooled estimate including all studies was 13.7% (95% CI, 10.6%-18.1%) with significant heterogeneity p = <0.001 and I^2 at 94.8% (Table 4.5). Figure 4.29 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with ≥85% J-pouch had lower rates of pad use, 6.0% (95% CI, 2.1%-16.5%). Restricting the analysis to studies with at least 5 years of follow-up had little effect on the summary estimate, while studies with <10% lost to follow-up had slightly higher rate of pad use, as did studies with ≥85% diverting ileostomy (Table 4.6). At the study level, proportion of J-pouch (p = 0.02, Figure 4.30) was associated with a decrease rate of pad use, accounting for 23.56% of between study variability. Funnel plot of the rate of pad use on the log scale plotted against study size reveals evidence of publication bias with few small studies being published with higher rates of pad use (Figure 4.31).
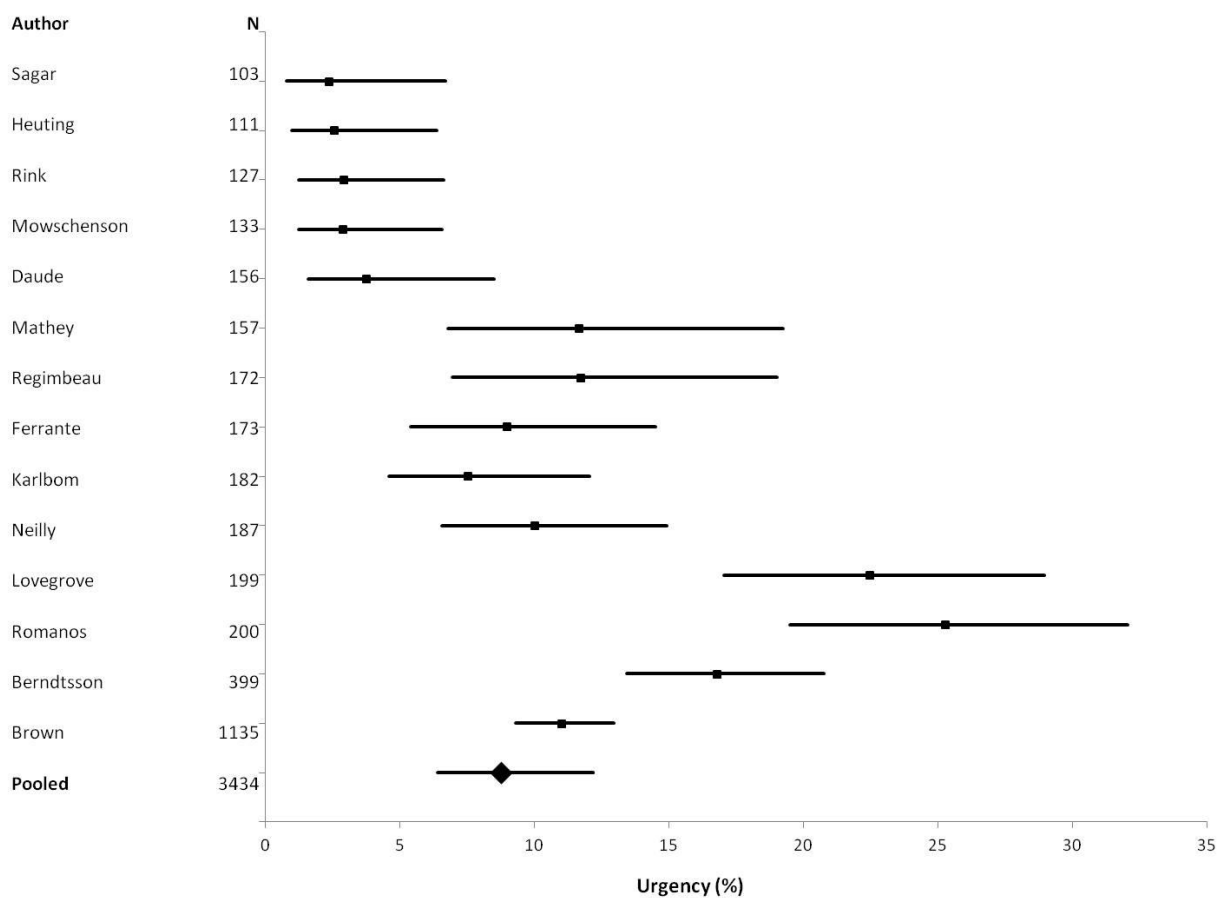
Figure 4.29 Forrest plot of studies reporting on rates of pad use. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
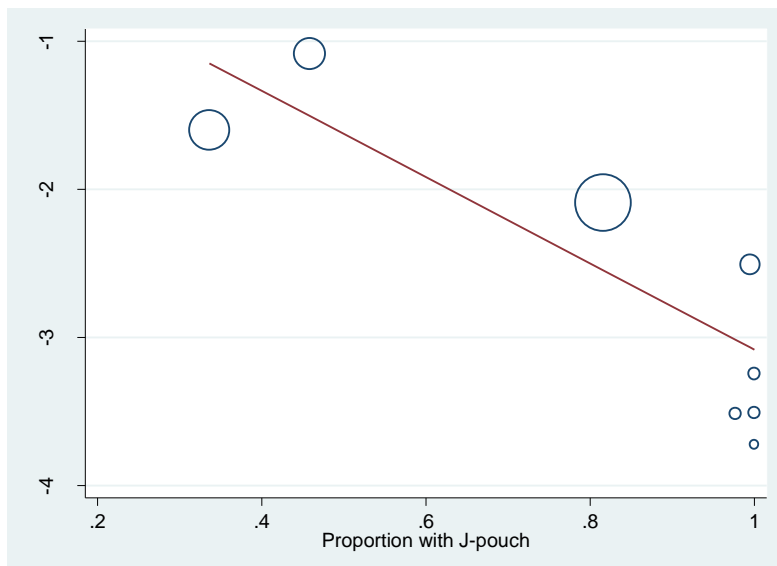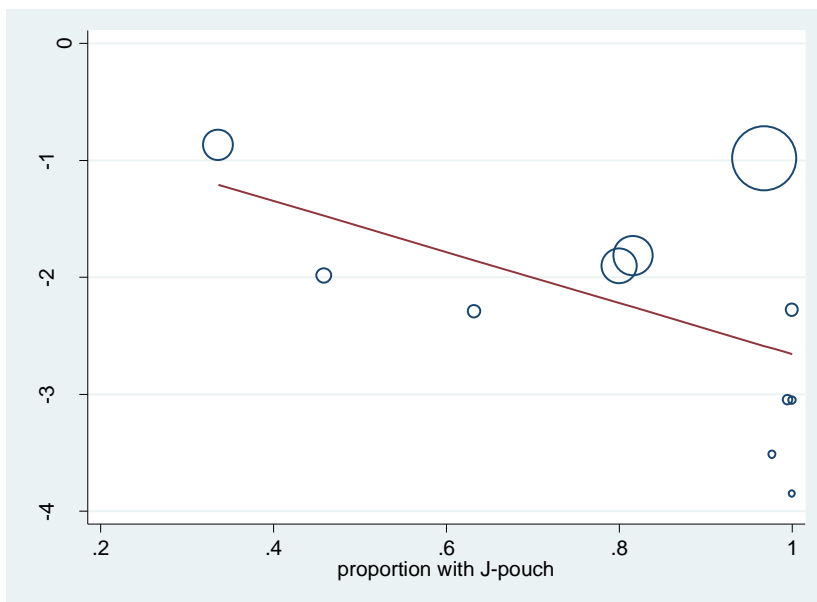
Figure 4.30 Meta-regression of proportion of patients with J-pouch on rate of pad use (ln(odds)). Studies with a higher proportion of J-pouch reported lower rates of pad use, accounting for 23.56% of between study variability (p = 0.02). The area of the circle is proportional to the number of patients in each study.
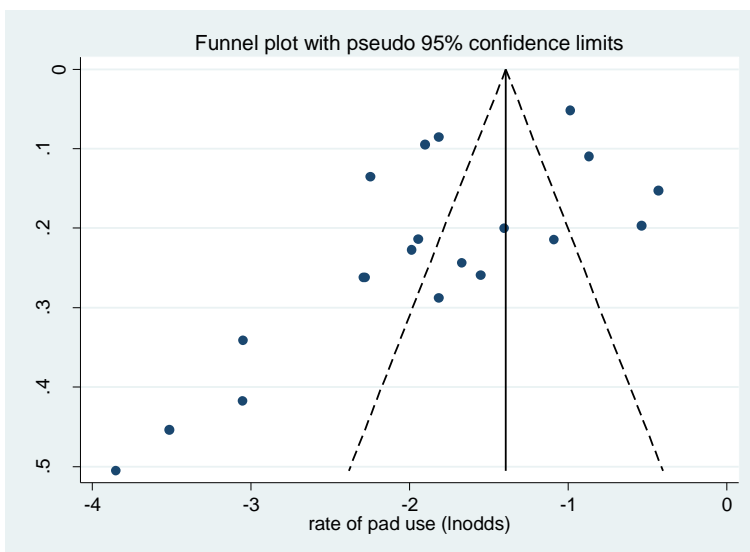
Figure 4.31 Funnel plot showing rate of pad use (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of pad use.

Anti-Diarrheal Medication Use

Twenty-four studies totaling 6,153 patients reported on the rates of anti-diarrheal (AD) medication use, with individual study estimates ranging between 12.6%-60%[26-30, 32, 33, 37, 39, 43, 44, 47, 50, 52, 58, 64, 70, 78, 81, 83, 86, 89, 91, 93]. The pooled estimate including all studies was 32.9% (95% CI, 27.3%-39.4%) with significant heterogeneity p = <0.001 and I^2 at 95.1% (Table 4.5). Figure 4.32 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. There was little difference between the rates of AD medication use among subgroups (Table 4.6). Similarly, no study level factors were significantly associated with differences in the rate of AD medication use during meta-regression. Funnel plot of the rate of AD medication use on the log scale plotted against study size reveals no asymmetry to suggest publication bias (Figure 4.33).
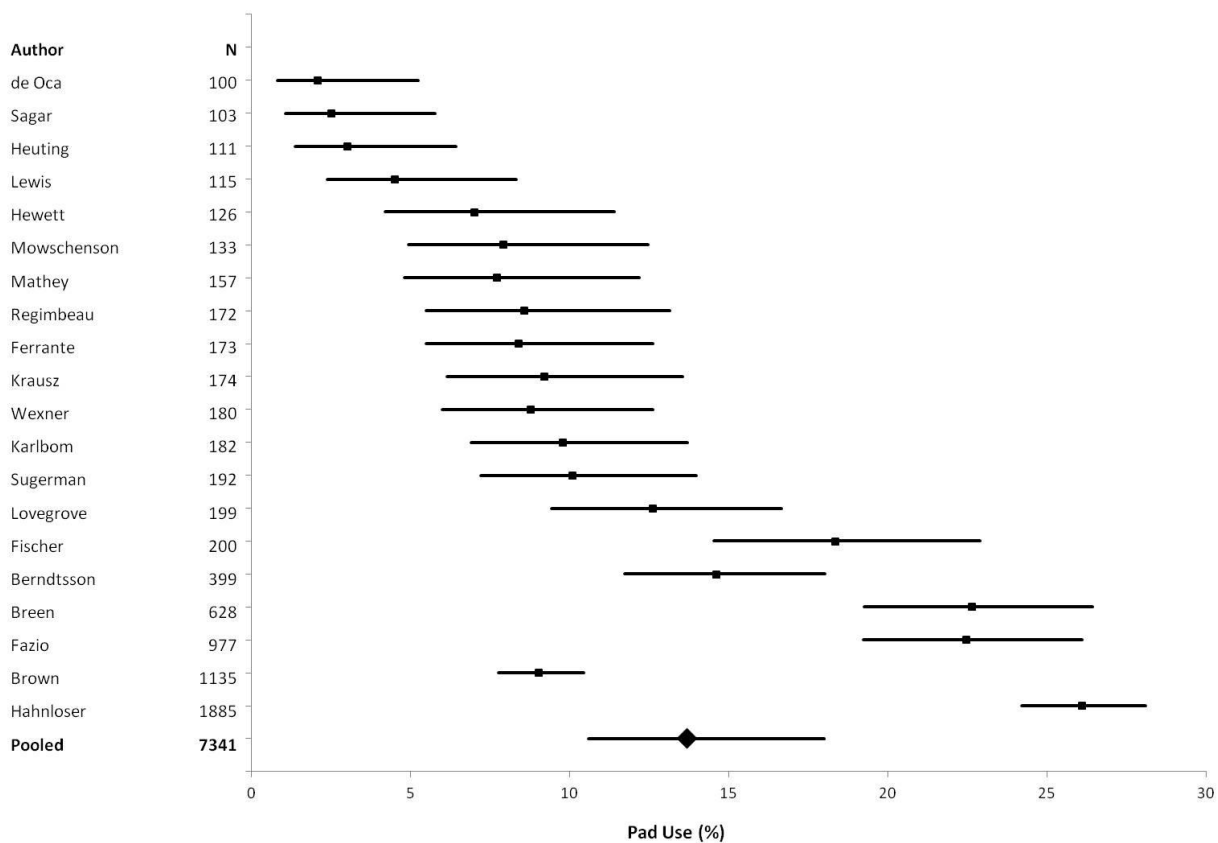
Figure 4.32 Forrest plot of studies reporting on rates of AD medication use. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
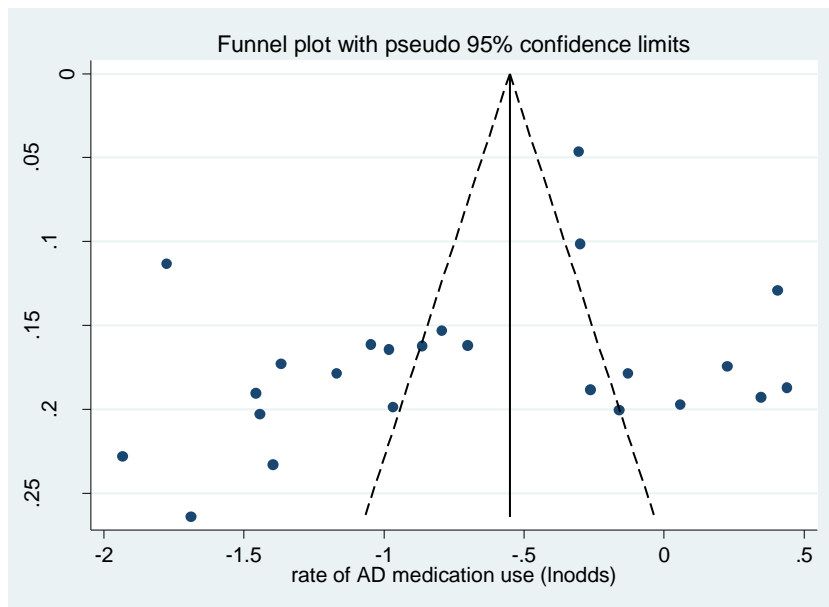

Figure 4.33 Funnel plot showing rate of AD medication use (ln(odds)) against study size. No evidence of asymmetry to suggest publication bias.

Mean Number of Bowel Movements/ 24 hours

Twenty seven studies totaling 8,336 patients reported on the mean number of bowel movements (BM) within 24 hours, with individual study estimates ranging between 4.2-7.8 BM/24hrs[25, 27-30, 32, 35, 40, 43, 44, 46, 47, 52-54, 58, 59, 63, 64, 68, 76, 78, 81, 83, 89, 91, 93]. The pooled estimate including all studies was 5.6 BM/24 hrs (95% CI, 5.3-5.9) with significant heterogeneity p = <0.001 and I^2 at 99.1% (Table 4.5). Figure 4.34 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Studies with ≥85% J-pouch and with follow up of at least 5 years both had slightly higher mean number of BM/ 24hrs, 6.1 (95% CI,5.6-6.5) and 5.8 (95% CI, 5.5-6.1) respectively. Restricting the analysis to studies with ≥85% diverting ileostomy and < 10% follow-up had little effect on the summary estimate (Table 4.6). At the study level, proportion of J-pouch (p = 0.01, Figure 4.35) was associated with a higher mean number of BM/24 hrs, accounting for 17.02% of between study variability, while study type and mid-point year lost their association with multivariable meta-regression. Funnel plot of the mean number of BM/24 hrs against study size reveals evidence of publication bias with few small studies being published with higher mean number of BM/24 hrs (Figure 4.36).
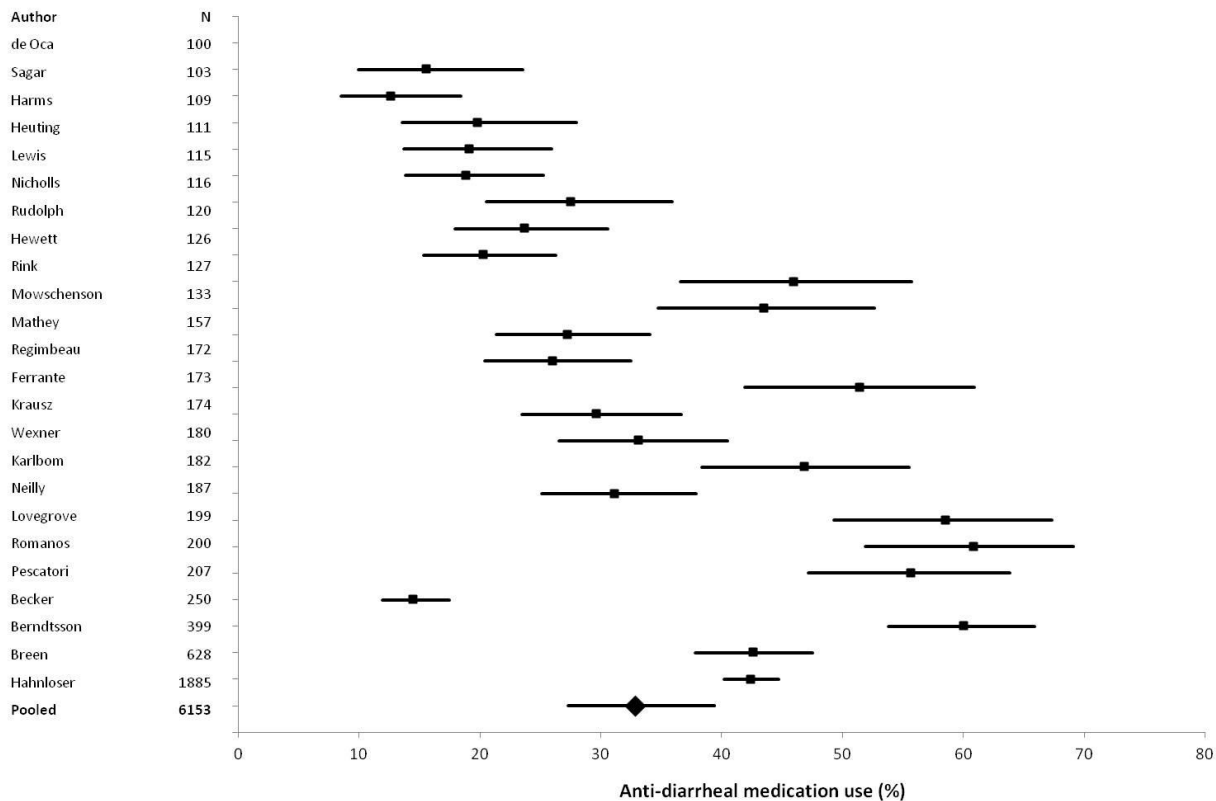
Figure 4.34 Forrest plot of studies reporting mean number of BM/ 24 hrs. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
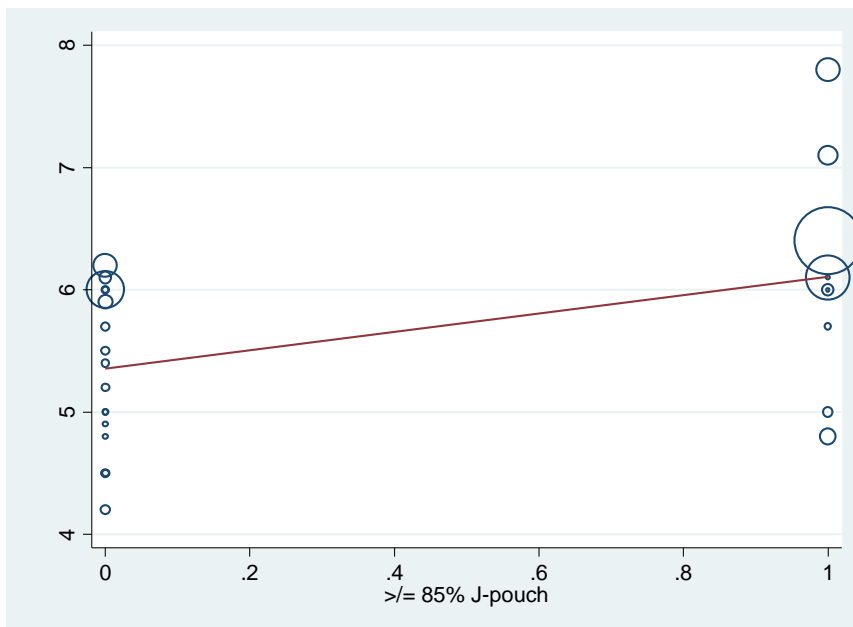
Figure 4.35 Meta-regression of studies with ≥85% J-pouch (0 =<85% J-pouch, 1 = ≥85% J-pouch) on mean number of BM/ 24hrs. Studies with a higher rate of J-pouch had more BM in 24hrs, accounting for 17.02% of between study variability (p = 0.01). The area of the circle is proportional to the number of patients in each study.
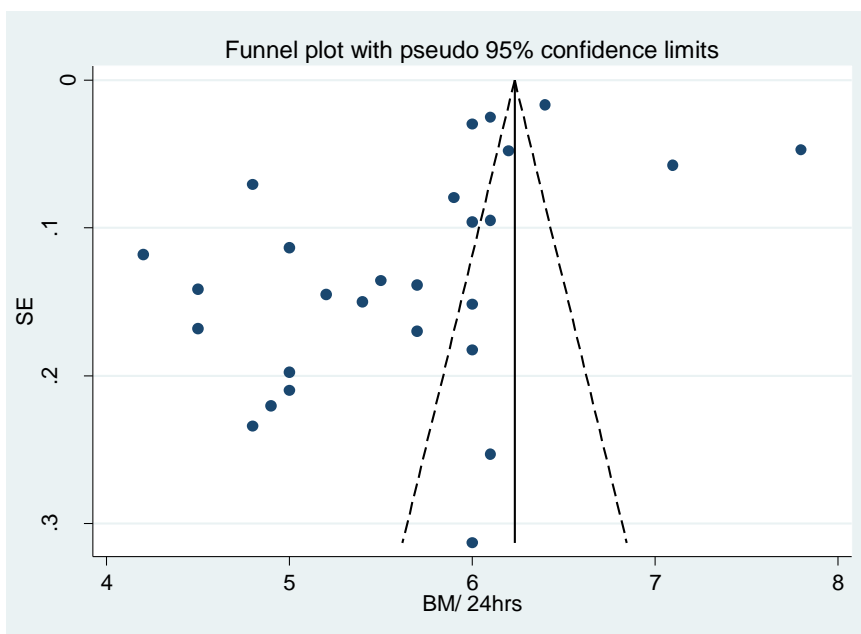
Figure 4.36 Funnel plot showing rate mean number of BM/ 24hrs against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher number of BM/24 hrs.

Mean Number of Bowel Movements/ Night

Fifteen studies totaling 5,594 patients reported on the mean number of bowel movements (BM) at night, with individual study estimates ranging between 0.3-1.7 BM/night[28-30, 35, 44, 46, 54, 58, 63, 64, 76, 78, 83, 89, 91]. The pooled estimate including all studies was 1.0 BM/night (95% CI, 0.8-1.2) with significant heterogeneity p = <0.001 and I^2 at 99.0% (Table 4.5). Figure 4.37 graphically summarizes each study estimate, its 95% confidence interval, and the pooled estimate. Subgroup analysis failed to reveal any differences in mean number of BM/ night (Table 4.6). Similarly, univariable meta-regression failed to identify any significant associations between study level factors and mean number of BM/night. Funnel plot of mean number of BM/night did not reveal any asymmetry to suggest publication bias.
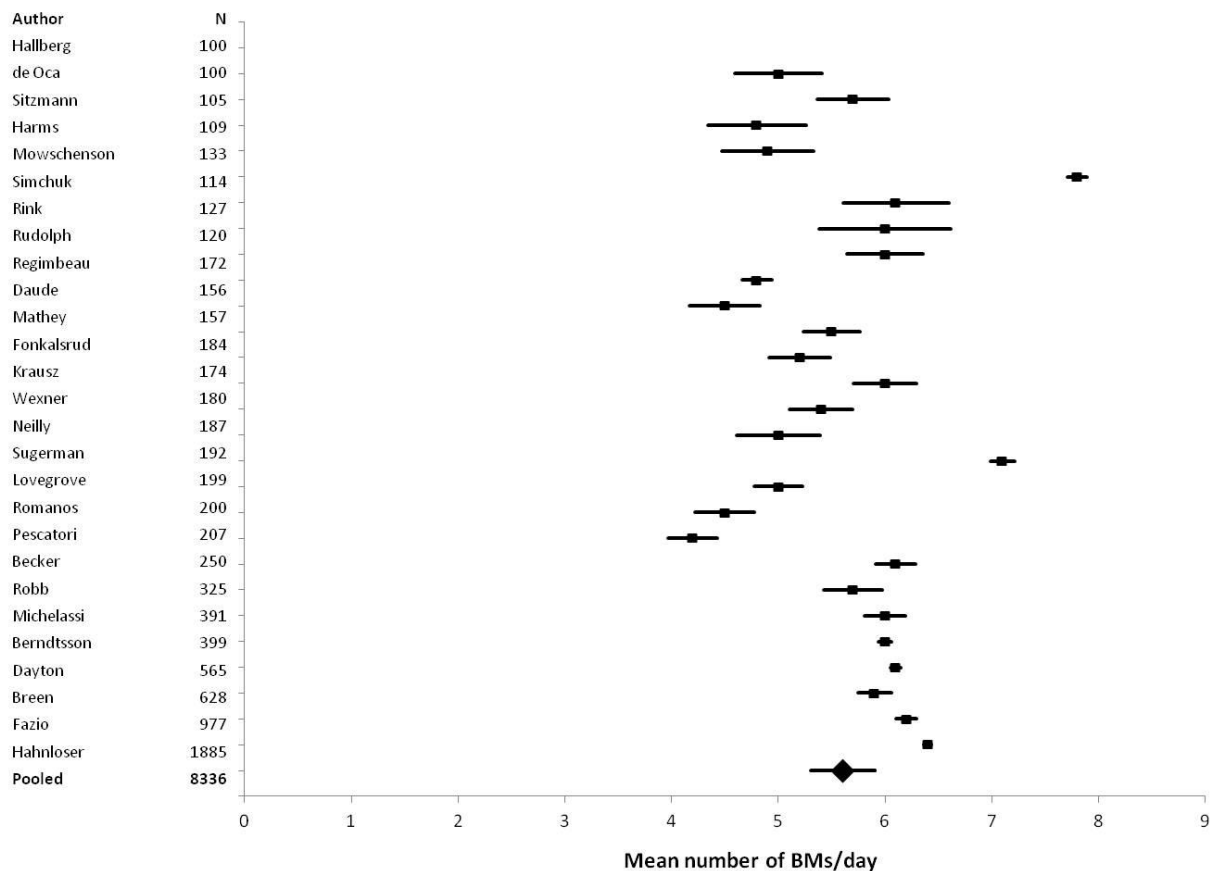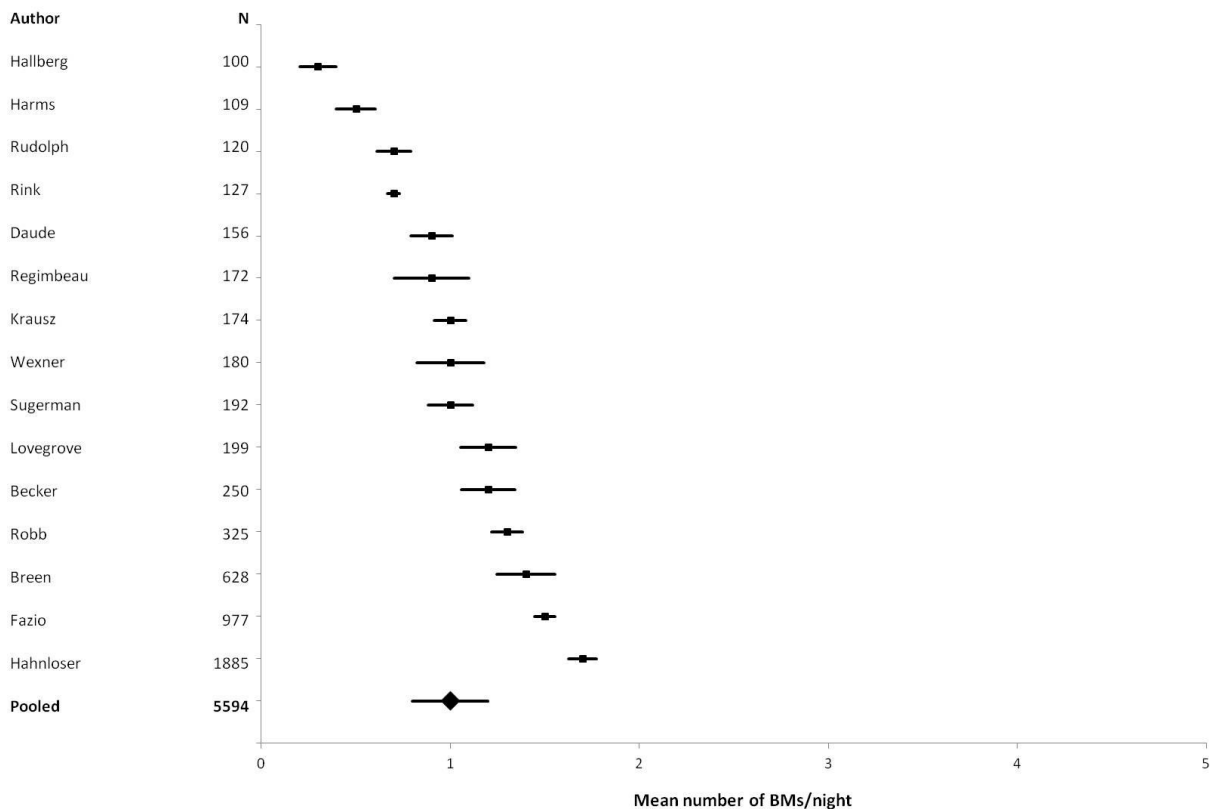
Figure 4.37 Forrest plot of studies reporting mean number of BM/ night. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
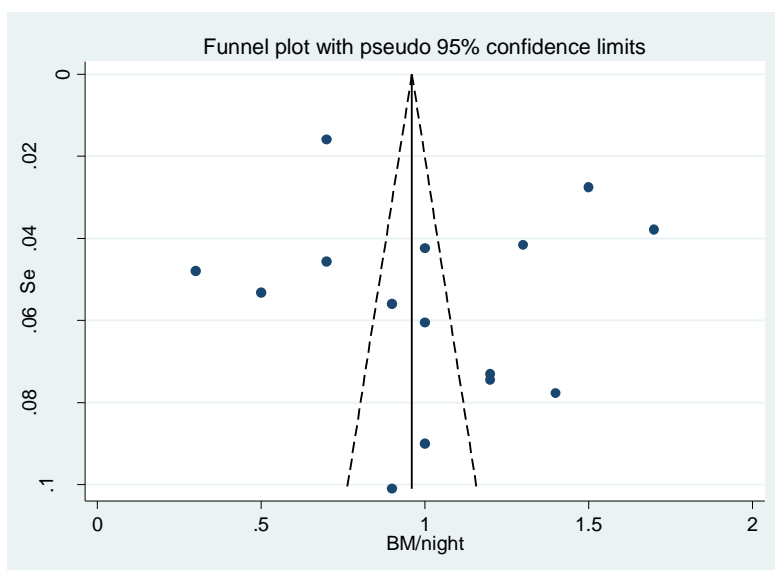

Figure 4.38 Funnel plot of mean number of BM/ night fails to reveal any significant asymmetry to suggest publication bias.

Table 4.5 Meta-Analysis of Functional Results Following IPAA

Function	Number of Studies	Number of Patients	Pooled %	95% CI	Heterogeneity I^2(%)	p
Fecal incontinence	30	9,284	13.2	9.9-17.3	96.9	<0.001
Urgency	14	3,434	8.8	6.4-12.2	88.2	<0.001
Pad use	20	7,341	13.7	10.6-18.1	94.8	<0.001
Anti-diarrheal meds	24	6,153	32.9	27.3-39.4	95.1	<0.001
Mean number of BM/24 hrs	27	8,336	5.6	5.3-5.9	99.1	<0.001
Mean number of BM/night	15	5,594	1.0	0.8-1.2	99.0	<0.001

BM bowel movements

Table 4.6 Subgroup Meta-Analysis of Functional Results Following IPAA

| Sub-Group	No. Studies	No. of Patients	Pooled %	95% CI	Heterogeneity I^2	p
≥85% J-pouch						
Fecal incontinence	8	3,350	9.1	3.3-24.5	98.4	<0.001
Fecal urgency	5	804	3.9	2.4-6.4	47.8	<0.001
Daily pad use	6	2,754	6.0	2.1-16.5	96.3	<0.001
Anti-diarrheal medication	6	2,689	35.2	27.6-43.7	90.7	<0.001
Mean number of BM/24hrs	10	3,878	6.1	5.6-6.5	97.1	<0.001
Mean number of BM/night	6	2,675	1.1	0.8-1.4	98.8	<0.001
≥85% Diverting ileostomy						
Fecal incontinence	13	5,074	14.9	9.4-22.9	97.7	<0.001
Fecal urgency	4	589	5.7	2.8-11.5	76.5	<0.001
Daily pad use	11	4,702	15.8	11.3-21.8	94.8	<0.001
Anti-diarrheal medication	12	4,091	29.6	21.3-39.6	96.8	<0.001
Mean number of BM/24hrs	17	6,288	5.4	5.2-5.7	99.1	<0.001
Mean number of BM/night	10	4,856	1.1	0.8-1.4	98.8	<0.001
Follow-up ≥ 5yrs						
Fecal incontinence	9	5,362	15.9	9.6-25.4	98.4	<0.001
Fecal urgency	5	2,066	9.8	5.8-16.1	91.7	<0.001
Daily pad use	10	5,387	13.7	9.4-19.5	90.1	<0.001
Anti-diarrheal medication	8	3,270	29.9	22.8-38.0	93.8	<0.001
Mean number of BM/24hrs	11	5,156	5.8	5.5-6.1	98.9	<0.001
Mean number of BM/night	6	3,905	1.1	0.9-1.4	97.7	<0.001
< 10% lost to follow-up						
Fecal incontinence	20	7,029	13.8	9.5-19.7	97.5	<0.001
Fecal urgency	9	2,661	11.5	6.4-12.2	88.7	<0.001
Daily pad use	10	5,000	17.1	12.2-23.5	95.8	<0.001
Anti-diarrheal medication	15	4,774	32.2	25.2-39.9	95.8	<0.001
Mean number of BM/24hrs	14	4,851	5.5	5.3-5.8	97.8	<0.001
Mean number of BM/night	8	3,455	1.0	0.6-1.4	99.5	<0.001

4.3 Discussion

This systematic review summarizes the literature reporting on clinical outcomes following IPAA, and includes 67 studies reporting on 21,882 patients. These studies varied greatly in their patient characteristics, operative approaches, and methodologic rigor. In an attempt to account for the significant between study heterogeneity, we carried out multiple sensitivity analyses and meta-regressions along both clinical variables and methodologic criteria.

One of the most severe complications following this procedure is pouch failure resulting in pouch removal and/or permanent ileostomy. The pooled incidence was 5.5%, which was significantly lower amongst those studies which predominantly reported on patients with J-pouch configuration (pooled incidence 3.8%), and higher amongst those studies with at least five years of follow-up (6.3%). No doubt as length of follow-up increases, so does the rate of pouch failure as patients may develop pouchitis over time necessitating diversion or pouch removal. The influence of pouch type on results was also seen for functional outcomes. Studies reporting on patients with J-pouch configuration (as opposed to a S- or W- pouch) had improved pouch function as evidenced by lower rates of fecal incontinence, fecal urgency, and daily pad use when compared to other studies using meta-regression. This finding is supported by a meta-analysis looking specifically at pouch configuration that found the J-pouch had higher number of BM/ day but lower rates of other complications[95]. Similarly, the mean number of bowel movements per 24 hours among studies reporting on patients with J-pouch configuration was significantly higher than those reporting on other pouch configurations with a mean

of 6.1 BM/24 hrs among those with J-pouch. Given that most surgeons now use the J-pouch configuration and that a consistent association with this subgroup and most functional outcomes reported in this anaysis was observed, we decided to use this subgroup of studies to populate our decision aid with functional outcomes.

Of the methodologic criteria examined using meta-regression, outcome definition was consistently associated with an increase in complication rates for most of the clinical outcomes (pouch fistula, anastomotic stricture, pouchitis, and small bowel obstruction). This implies that studies using well defined outcome criteria are capturing more patients with those complications. This likely protects against reporting bias by standardizing the assessment of the outcomes and resulting in more reliable complication rates. Other methodologic criteria including prospective design, consecutive patient recruitment, proportion loss to follow-up, and use of a standardized follow-up protocol were not consistently found to influence the rate of complications reported in individual studies. There is no empiric evidence available to guide the selection of quality criteria when assessing observational studies[6, 7], although with this analysis we have shown a consistent association between the use of clearly defined outcome criteria and rate of most complications reported in these studies. Thus, outcome criteria definition should be strongly considered as a quality measure when assessing observational studies reporting on complications following surgery.

Other study level factors we explored using meta-regression included proportion of patients with Crohn's disease, indeterminate colitis, and FAP. Proportions of these alternate diagnoses among studies were not associated with rates of outcomes. Studies designed to specifically look at the influence of these other diagnoses on the results of

restorative pouch procedures have documented higher rates of complications in patients with Crohn's disease and indeterminate colitis[75]. In a meta-analysis looking specifically at patients with Crohn's disease who had undergone a restorative pouch procedure, the failure rate was 32%[96].Despite a strong association with outcomes in other studies, prevalence of Crohn`s disease was not associated with outcomes during our meta-regression. This lack of association seen at the study level likely reflects the low prevalence of Crohn's disease among the studies included with only 18 of 67 studies including patients with Crohn's disease and of those most accounted for <5% of patients. Similarly, the proportion of patients with FAP and indeterminate colitis in the included studies was low as well.

Study level factors dealing with operative technique examined with meta-regression included proportion of patients who received a stapled anastomosis and proportion of patients with defunctioning ileostomy. No association at the study level between the proportion of patients with a defunctioning ileostomy and complication rates was identified. A meta-analysis of observational studies comparing patients with and without diversion did show that patients who forgo diversion are at increased risk of pouch-related septic complications[22]. Most studies included in this review reported 80% or greater rates of diversion, thus the un-diverted group likely account for too few patients to affect the results. Similarly, no association was found between the proportion of patients who underwent a stapled anastomosis and complication rates.

Comparing our results to those of the only other systematic review and meta-analysis of IPAA studies, our overall pooled rates of complications tended to be slightly less than that reported by Hueting et al.[3] For example, our pooled rate of pouch failure

was 5.5% versus 6.8% in the former review. This could be the result of our study focusing on larger patient series (100 or greater patients) or more modern series, as their review was limited to studies published up to 2000. As surgeons gain experience, results will improve and this may be a reflection of this. Other complex surgical procedures have been found to have a volume-outcome relationship, with better outcomes arising amongst those surgeons with higher volumes[97, 98]. Our review not only updates that of the previous authors, but includes an in-depth analysis of between study heterogeneity utilizing subgroup analysis, meta-regression, and funnel plots to examine for publication bias.

With the exception of use of anti-diarrheal medications and mean number of BM/ night, every outcome studied showed evidence of publication bias with smaller studies predominantly reporting on lower complication rates. Presumably, this results from the difficulty or unwillingness to publish smaller studies with poorer results, similar to negative comparative trials[99]. By using a random effects model to combine complication rates, studies were weighted based on a combination of within study and between study variability. Given the high degree of between study variability, smaller studies are given more relative weight then they would if the between study variability were less, with weights more reflective of study size. This in combination with the lack of smaller studies reporting higher complication rates probably lead to an under-estimation of true pooled complication rates.

One way to deal with this problem is to restrict the meta-analysis to larger studies whose outcome distributions are more symmetrical[10]. We conducted a sensitivity analysis of all outcomes on study size by comparing studies with at least 250 patients to those with 100-249 patients and found little difference in pooled outcomes. For example, the

pooled pouch failure rate amongst studies with ≥ 250 patients was 5.2% (95% CI, 4.4-6.1) and 5.6% (95% CI, 4.5-6.9) among those with 100-249 patients. This indicates that although the funnel plots suggest publication bias, the degree of between study heterogeneity likely outweighs any influence publication bias has on the summary estimates. This can be visualized by the number of studies that fall outside the 95% confidence limits of the funnel plots (Figure 4.3) which occurs over the entire plot, not just at the base.

Other methods do exist to adjust for the presence of publication bias. Methods based on regression equations and adjustment of summary estimates have been developed, however they have been found to perform poorly when the I^2 value reaches 50%, and thus were not used in this study[100]. Although the funnel plots suggest publication bias for most outcomes, with fewer small studies reporting on higher complication rates following IPAA, the degree of between study heterogeneity exerts a much larger influence on pooled outcomes.

Along with pouch failure, one of the more significant complications following IPAA is pouchitis. Characterized by poor pouch function, pain, urgency, and multiple bloody bowel movements, this complication can be detrimental to a patient's quality of life[101]. The pooled rate of pouchitis was 22%, with individual study ranges from 2-60%. When study level factors were explored, the rate of pouchitis was higher among studies with at least five years of follow-up (28%) and among studies that utilized clearly defined outcome criteria (28%). We were not able to evaluate what specific criteria were used to define pouchitis in each individual study as they varied greatly, from no criteria to rigorous programs involving endoscopic surveillance and biopsies of the pouch. This

highlights one of the limitations of this meta-analysis and likely accounts for some of the residual between study heterogeneity that we were unable to account for despite sensitivity analyses and meta-regressions. Studies using different outcome criteria will result in varying rates of pouchitis, as with other outcomes. The challenge we faced was our desire to summarize the literature into point estimates that we could include into a decision aid for patients, while running the risk of combining studies that were measuring different things. As evidenced by the large I^2 values, even after sensitivity analyses and meta-regression, there clearly remains significant between-study heterogeneity, likely the result of un-accounted for study level differences in specific outcome criteria, population parameters, and study design.

Despite its utility in exploring heterogeneity and guiding our selection of which group of studies to include in our decision aid, meta-regression is not without its own limitations and cautions. A major limitation is that meta-regression of observational trials are still limited by the quality and potential bias inherent in the individual trials[24]. Another caution is the use of meta-regression to identify associations between study level factors and use this to imply an association at the patient level, a situation known as aggregation bias or ecological fallacy[102]. For example, if we had identified an association between a higher proportion of diverted patients and pelvic sepsis, then we may have concluded that diversion results in a higher risk of pelvic sepsis, when in actual fact, at the patient level, all the patients in the studies that had this complication were in the un-diverted group and differences in other risk factors accounted for the study level association. This type of bias is difficult to detect without patient level data, and thus any patient level causal inferences made on the basis of study level associations must be

viewed with caution[103]. Another limitation of meta-regression is that it often suffers from low power, due to smaller numbers of included studies[103]. To combat this, most authors recommend that no more than 1 study level covariate be explored for every 10 studies in the meta-analysis[24, 103]. This ratio was used to guide the number of covariates we included in our multivariable meta-regression. Another limitation is the potential for data dredging and multiplicative testing with possible false positive associations. Most authors recommend pre-specifying the covariates to be examined, as we did in this study. Another strategy is to apply a Bonferroni adjustment to the significance level[24] of each covariate. We elected not to do this as we had pre-specified our covariates of interest, and our analyses were exploratory in nature, trying to explain heterogeneity, not to make causal inferences. At the statistical level, certain considerations are important to properly conduct a meta-regression. We used a random-effects meta-regression which accounts for both between study and within study variance, this the recommend approach as no set of covariates will completely explain all the heterogeneity present, thus this must be accounted for in the analysis[24].

No established protocol exists for the selection of which studies to include when conducting a meta-analysis with a view towards populating a decision aid with outcome estimates. We applied a systematic assessment of between study heterogeneity using subgroup analyses and meta-regression in an effort to guide the selection of appropriate studies to include in the summary estimate destine to be included in the decision aid. For those outcomes that were significantly influenced by length of follow-up (pouch failure, pouchitis) these point estimates were used, while for studies that showed an association with outcome definition (pouch fistula, anastomotic stricture, small bowel obstruction)

these subgroups were used. Pelvic sepsis showed an association with prospective design, and this was selected as the group for that outcome. While functional results were taken from the subgroup of studies reporting on 85% or greater J-pouch patients as there was a consistent association with functional outcomes and this subgroup in the meta-regression.

Despite significant residual between-study heterogeneity, we executed a large, inclusive review with systematic and rigorous exploration of heterogeneity that revealed a consistent association with outcome criteria definition and complication rates, thus adding some empiric evidence to its use as a quality criterion for the reporting of observational surgical trials. We also used the results of the meta-regression to guide the inclusion of studies into the decision aid's point estimates. The next chapter will summarize the systematic review of studies reporting on the outcomes following ileostomy, while chapter six will outline the methodology necessary in the refinement and initial testing of the prototype decision aid.

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CHAPTER FIVE-SYSTEMATIC REVIEW AND META-ANALYSIS OF OUTCOMES FOLLOWING PROCTOCOLECTOMY AND ILEOSTOMY

5.0 Introduction

The traditional option for patients with ulcerative colitis requiring surgery is total proctocolectomy and end-ileostomy. This technique involves suturing the end of the small bowel (the ileum) to the skin and everting it along the fashion described by Brooke, in an effort to minimize skin based complications[1]. This is touted as the gold standard for the management of ulcerative colitis and has been performed since the 1950's. Despite its long history and successful track record, this procedure is not without its own share of long-term problems, largely the result of complications related to the ileostomy. In order to provide patients with information necessary to decide between having an ileostomy or a restorative pouch procedure, it is necessary to summarize the risks of a long-term ileostomy. In order to populate our decision aid, we undertook a systematic review and meta-analysis of outcomes following protcolectomy and ileostomy with a focus on ileostomy-based complications. This information is important to patients who are deciding between living with a long-term ileostomy or contemplating conversion to a restorative pouch procedure. An ileostomy, although technically simple to construct, is fraught with numerous long-term problems which must be balanced by the risks of IPAA when patients are deciding between the two options.

5.1 Methods

Search Strategy

The overall search strategy is outlined in chapter two of this work. We included studies reporting on outcomes following colectomy and ileostomy for patients with ulcerative colitis who reported on at least 100 patients. All titles and abstracts were independently reviewed by two reviewers and any study that either reviewer deemed as potentially eligible was selected for full text review. Study inclusion was then assessed independently with any disagreement resolved by consensus.

Data Extraction

Full text papers were reviewed, and for all studies that met our inclusion criteria, data was extracted independently by two reviewers with any disagreement resolved by consensus using standardized data-abstraction sheets. Study characteristics including size, location, time period of patient enrollment, length of follow-up, mean age of patients, proportion with Crohn's disease, FAP, or indeterminate colitis, proportion with prior subtotal colectomy, and proportion with excision of rectum were abstracted. Outcomes of interest included ileostomy revision (any procedure undertaken to revise the ileostomy regardless of method or indication), ileostomy stenosis, ileostomy prolapsed, ileostomy fistula, ileostomy retraction, small bowel obstruction requiring surgery, and parastomal hernia requiring surgery.

Quality Criteria

A detailed discussion of the rationale behind the selection of quality criteria is found in chapter two of this work. We selected specific elements of study design reflective of quality and reported on them rather than used established tools as there is no

empirical evidence linking any one tool or set of criteria to study validity for

observational studies[2, 3]. The elements of quality examined included: whether or not the

patients represented a group of consecutive patients having surgery over a pre-specified

time period, whether the authors used clearly defined outcome criteria, whether the study

was retrospective or prospective, proportion loss to follow-up, and whether they

employed a standardized follow-up procedure.

Meta-Analysis

Each study estimate of a given outcome was recorded and its 95% confidence

interval was determined using Wilson's score method[4]. In order to combine the

proportions from individual studies, we converted the individual proportions into odds[5],

and the odds was transformed into the log scale using equation 4.1:

ln(odds) = ln (no of patients having event/ no of patients not having event)   (4.1)

This allowed us to generate a variance term which was used in the weighting of studies

for the meta-analysis(equation 4.2):

var ln(odds) = 1/No of patients having event + 1/ no of patients not having event[5]   (4.2).

Meta-analysis was then carried out of individual study proportions converted to

the ln(odds) scale according to the random-effects model of DerSimonian and Laird[6],

accounting for both within-study variance and between-study variance. This model

assumes that the outcome measures of each study come from a random distribution of

outcomes, with the weighting of studies based on the reciprocal of the sum of between

study variance and within study variance. The statistical package, STATA version 10

(*Stata inc,* Texas, US, 2008) using the procedures *meta* and *metan* were used to meta-analysis the data as described by Sharp[7]. This procedure estimates the between-study variance using the non-iterative weighted method of DerSimonian and Laird[6]. Pooled results were converted back to the proportion scale and presented along with their 95% confidence interval. In case were the study had no events, a continuity correction factor was added (0.5) in order to generate an outcome measure for the meta-analysis as ln(0) is not a real number. Adding a continuity correction is preferred over excluding studies with zero events[8]. Each outcome was also graphically summarized using Forrest plots. The possibility of publication bias was explored using funnel plots of the individual outcomes, looking for asymmetry amongst the smaller trials. This was done assuming smaller trials might be more apt to get published if they have "better" results, ie lower rates of complications following surgery.

Heterogeneity

Heterogeneity was assessed for each outcome using the Cochran's Q chi-squared test which is calculated by adding together the squared deviations of each study's outcome from the overall pooled outcome, adjusting each deviation by the study's weight used in the meta-analysis[9]. The degree of heterogeneity was also quantified using the I^2 statistic, which is the percentage of total variation across studies that is due to heterogeneity rather than chance[10]. The resulting value ranges from 0 (no heterogeneity) to 100, with an increasing amount of heterogeneity as the % I^2 increases. There were too few studies to conduct any meaningful subgroup analyses or meta-regression.

5.2 Results

5.2.1 Study Selection

We reviewed 3,920 abstracts and titles, of which 411 were selected for full-text review. Of these, 11 reported on the outcomes of colectomy and end-ileostomy for patients with ulcerative colitis. Agreement between reviewers for this subset of studies was excellent ($k = 0.78$).

5.2.2 Study Description and Quality

The 11 studies included 3,859 patients from five different countries, reporting on patients operated on from 1950 to 2005. Most of the studies were retrospective in nature and were of non-consecutive patients (Table 5.1). Two of the studies reported on the results of patient questionnaires, one from the US and the other from Australia. Only one study was prospective and it was also the only study with a standardized follow-up protocol. Only 3 of the 11 studies defined some of their outcome criteria, and length of follow-up was only recorded in three studies, with mean follow-up of 96, 110, and 139 months (Table 5.2). Only four of the studies reported exclusively on patients with ulcerative colitis. Patients with Crohn's disease were included in 6 studies with proportions ranging from 9.1% to 39.3%, while 3 studies included patients with FAP, ranging from 1.3% to 4%. Of the 11 studies, 6 studies exclusively reported on the results of total proctocolectomy, while two studies reported on the results of subtotal colectomy and ileostomy. The rate of proctocolectomy varied from 54.7% to 90.9% among the remaining three studies. Only two of the studies reported on loss to follow-up, the two patient questionnaire studies, which had response rates of 51.5% and 53.6%.

Table 5.1 Characteristics of Studies Reporting on Outcomes Following Colectomy and Ileostomy

Author	Location	Years of Surgery	Consecutive Patients	Type of Study	Outcome Defined	Standardized Follow-up
Morowitz and Kirsner[11], 1981	US (multiple states)	1960-1970	No	Patient Questionnaire	None	No
Albrechtsen et al[12], 1981	Oslo, Norway	1969-1978	No	Retrospective	Some	No
Bokey et al, 1984[13]	Sydney, Australia	1950-1981	No	Patient Questionnaire	None	No
Bauer et al[14], 1986	New York, US	1973-1984	No	Retrospective	Some	No
Berry et al[15], 1986	Oxford, UK	1972-1984	No	Retrospective	None	No
Carlstedt et al[16], 1987	Goteberg, Sweden	1959-1984	Yes	Prospective	None	Yes
Leong et al[17], 1994	London, UK	1971-1980	No	Retrospective	None	No
Leijonmarck et al, 1992[18]	Stockholm, Sweden	1955-1984	No	Retrospective	None	No
Carlsen and Bergan[19], 1995	Oslo, Norway	1980-1989	No	Retrospective	None	No
Karch et al[20], 1995	New York, US	1988-1993	Yes	Retrospective	None	No
Brady et a[21], 2008	Edinburgh, UK	1994-2005	Yes	Prospective	Some	No

Table 5.2 Characteristics of Patients in Studies Reporting on Ileostomy and Colectomy.

Author	N	Patient Mean Age (Range) y	% Crohn's	% FAP	% IC	% Removal of Rectum	% Prior-subtotal	Length of Follow-up (months)	Loss to Follow-up (%)
Morowitz and Kirsner[11], 1981	1803	35 (3-79)	0	0	0	70.5	NR	NR	51.5
Albrechtsen et al[12], 1981	154	34.7 (12-76)	0	0	0	90.9	0	NR	0
Bokey et al, 1984[13]	354	49	10	4	0	100	NR	NR	53.6
Bauer et al[14], 1986	427	NR	9.1	0	0	100	NR	NR	NR
Berry et al[15], 1986	115	33	23.5	0	0	100	18.3	NR	0
Carlstedt et al[16], 1987	104	34	0	0	0	100	NR	96	0
Leong et al[17], 1994	150	42 (14-76)	39.3	1.3	0	54.7	NR	110	NR
Leijonmarck et al, 1992[18]	255	NR	0	0	0	100	NR	139.2	0
Carlsen and Bergan[19], 1995	224	NR	24.1	3.5	0	100	NR	NR	NR
Karch et al[20], 1995	114	37 (13-79)	14.9	0	3.5	0	NR	NR	NR
Brady et a[21], 2008	159	41.9 (13-89)	0	0	0	0	NR	NR	NR

NR not recorded

5.2.3 Complications

Ileostomy Revision

Ten studies totaling 3,432 patients reported on the rate of ileostomy revision with individual study estimates ranging from 0.6% to 31.2%[11-13, 16-19]. The pooled estimate was 17.1% (95% CI, 13.1%-22.1%) with significant heterogeneity p = <0.001, I^2 at 86.4% (Table 5.3). Figure 5.1 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of revision within that study was 22.4%. Limiting the studies to ones that only reported on patients with ulcerative colitis resulted in a pooled rate of ileostomy revision of 14.5% (95%CI, 9.1%-22.2%) for 5 studies reporting on a total of 2,475 patients. A funnel plot (Figure 5.2) shows evidence of publication bias with fewer smaller studies being published with higher rates of ileostomy revision. Depending on the study the most common causes for revision were either stenosis or retraction of the ileostomy.
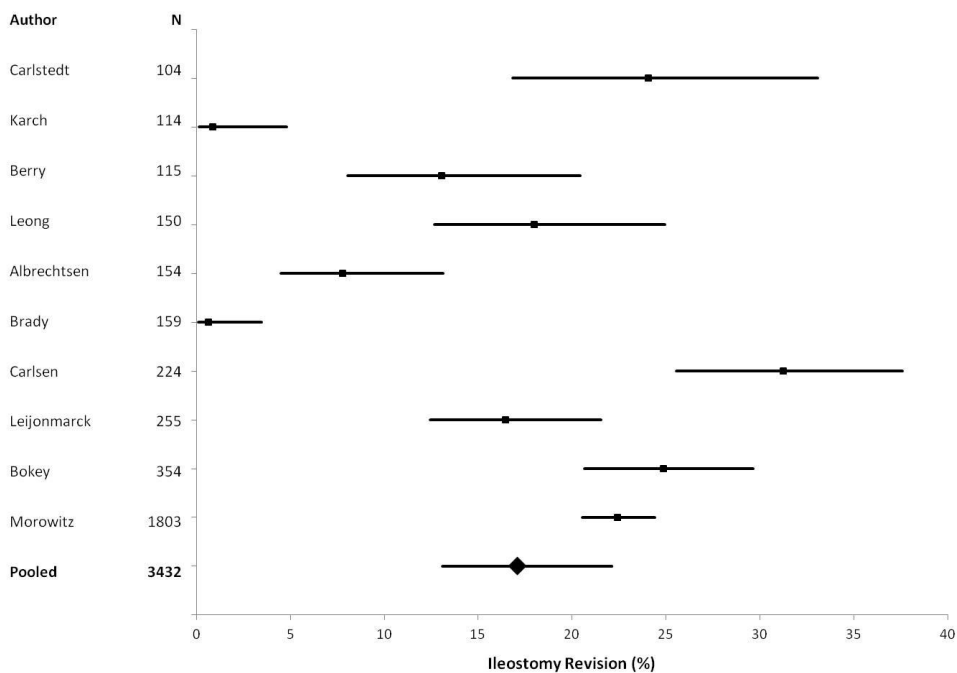
Figure 5.1 Forrest plot of studies reporting on rates of ileostomy revision. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
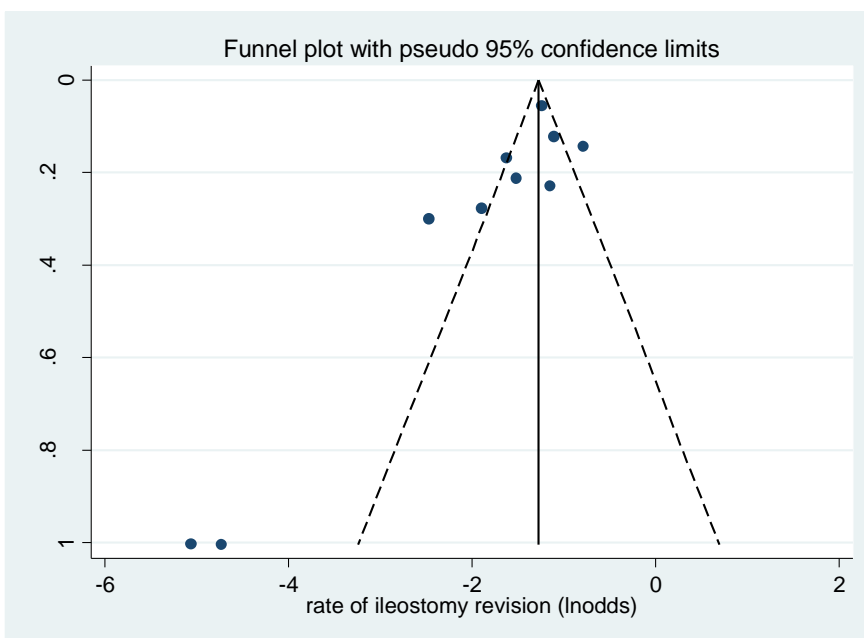

Figure 5.2 Funnel plot showing rate of ileostomy revision (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of ileostomy revision.

Ileostomy Stenosis

Seven studies totaling 3,044 patients reported on the rate of ileostomy stenosis requiring therapy with individual study estimates ranging from 0.6% to 13.5% [11-13, 15-21]. The pooled estimate was 5.7% (95% CI, 3.5%-9.5%) with significant heterogeneity p = <0.001, I^2 at 85.5% (Table 5.3). Figure 5.3 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of stenosis within that study was 5.6%. Limiting inclusion to studies that only reported on patients with ulcerative colitis resulted in a pooled rate of stenosis of 7.3% (95%CI, 3.9%-13.3%) for 4 studies reporting on a total of 2,316 patients. A funnel plot (Figure 5.4) shows evidence of publication bias with fewer smaller studies being published with higher rates of ileostomy stenosis.

Figure 5.3 Forrest plot of studies reporting on rates of ileostomy stenosis. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.

Figure 5.4 Funnel plot showing rate of ileostomy stenosis (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of ileostomy stenosis

Ileostomy Retraction

Six studies totalling 2,894 patients reported on the rate of ileostomy retraction, with individual study estimates ranging from 5.3% to 18.0% [11-13, 16, 18, 19]. The pooled estimate was 6.2% (95% CI, 2.7%-13.3%) with significant heterogeneity p = <0.001, I^2 at 95.0% (Table 5.3). Figure 5.5 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of ileostomy retraction within that study was 12.8%. Limiting inclusion to studies that only reported on patients with ulcerative colitis resulted in a pooled rate of retraction of 11.3% (95%CI, 6.1%-20.1%) for 4 studies reporting on a total of 2,316 patients. A funnel plot (Figure 5.6) shows evidence of publication bias with fewer smaller studies being published with higher rates of ileostomy retraction.
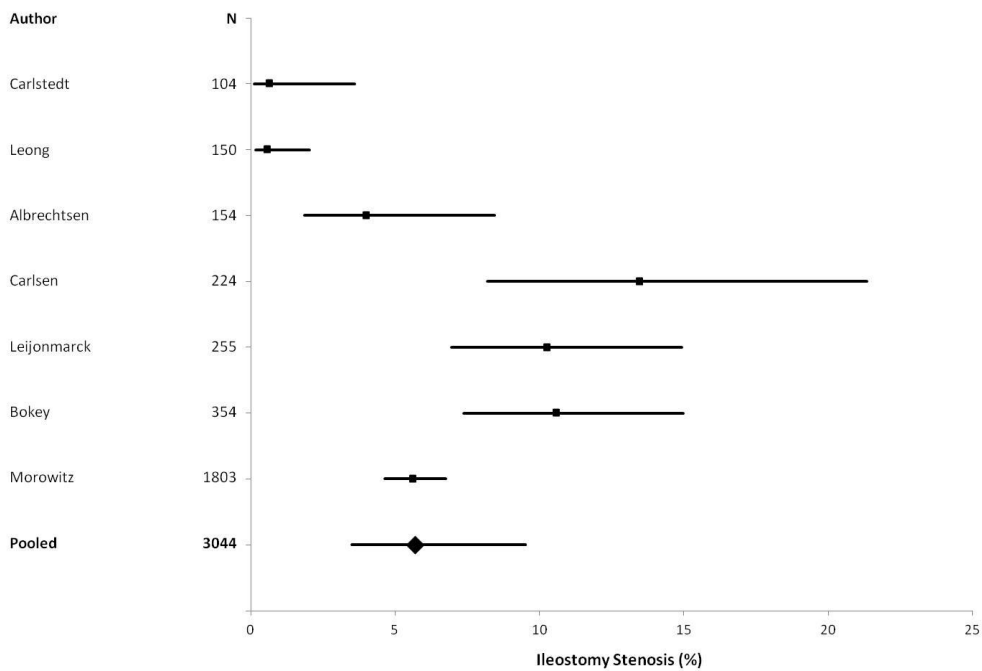
Figure 5.5 Forrest plot of studies reporting on rates of ileostomy retraction. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
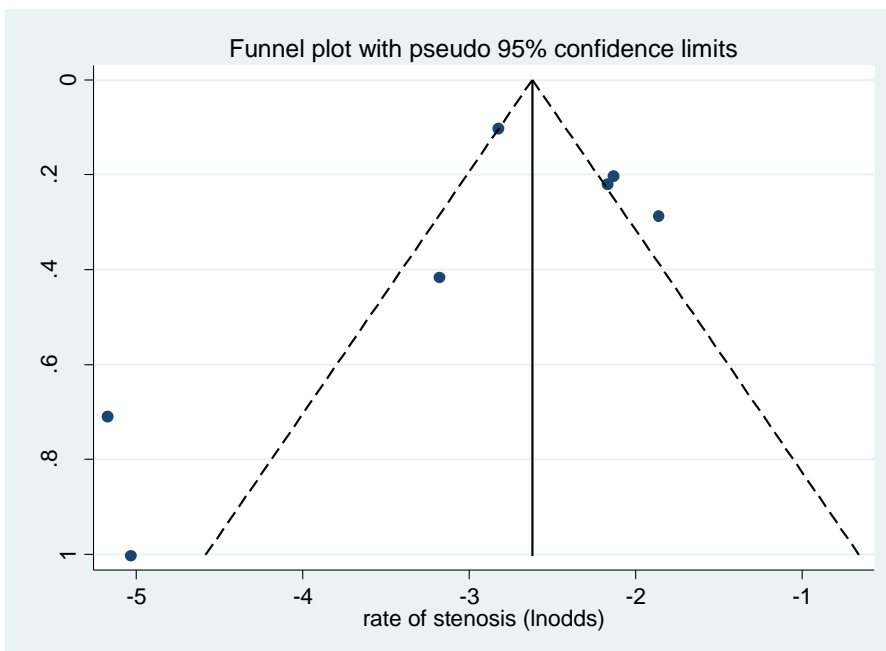

Figure 5.6 Funnel plot showing rate of ileostomy retraction (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of ileostomy retraction

Ileostomy Prolapse

Seven studies totalling 3,044 patients reported on the rate of ileostomy prolapse, with individual study estimates ranging from 0.6% to 10.5% [11-13, 16-19]. The pooled estimate was 3.1% (95% CI, 1.5%-6.4%) with significant heterogeneity p = <0.001, I^2 at 88.4% (Table 5.3). Figure 5.7 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of ileostomy prolapse within that study was 10.5%. Limiting the studies to ones that only reported on patients with ulcerative colitis resulted in a pooled rate of prolapse of 3.6% (95%CI, 1.4%-9.8%) for 4 studies reporting on a total of 2,316 patients. A funnel plot (Figure 5.8) shows evidence of publication bias with fewer smaller studies being published with higher rates of ileostomy prolapse.
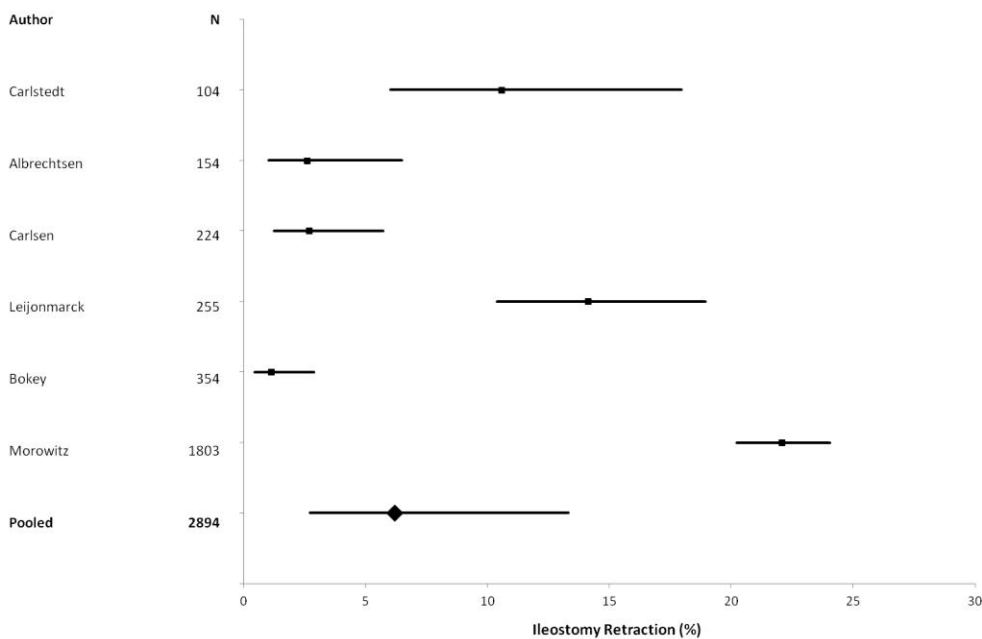
Figure 5.7 Forrest plot of studies reporting on rates of ileostomy prolapse. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
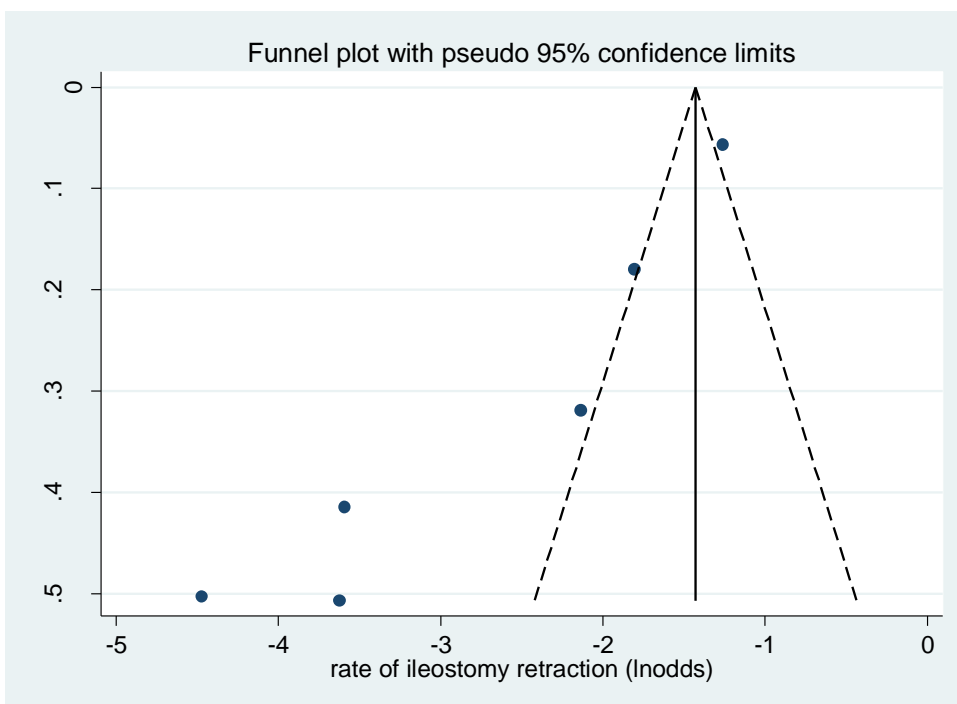

Figure 5.8 Funnel plot showing rate of ileostomy prolapse (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of ileostomy prolapse.

Ileostomy Fistula

Six studies totalling 2,940 patients reported on the rate of ileostomy fistula, with individual study estimates ranging from 0.6% to 9.4% [11-13, 17-19]. The pooled estimate was 4.8% (95% CI, 2.7%-8.3%) with significant heterogeneity p = <0.001, I^2 at 85% (Table 5.3). Figure 5.9 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of ileostomy fistula within that study was 9.0%. Limiting the studies to ones that only reported on patients with ulcerative colitis resulted in a pooled rate of ileostomy fistula of 3.1% (95%CI, 0.8%-8.3%) for 3 studies reporting on a total of 2,212 patients. A funnel plot (Figure 5.10) shows evidence of publication bias with fewer smaller studies being published with higher rates of ileostomy fistula.
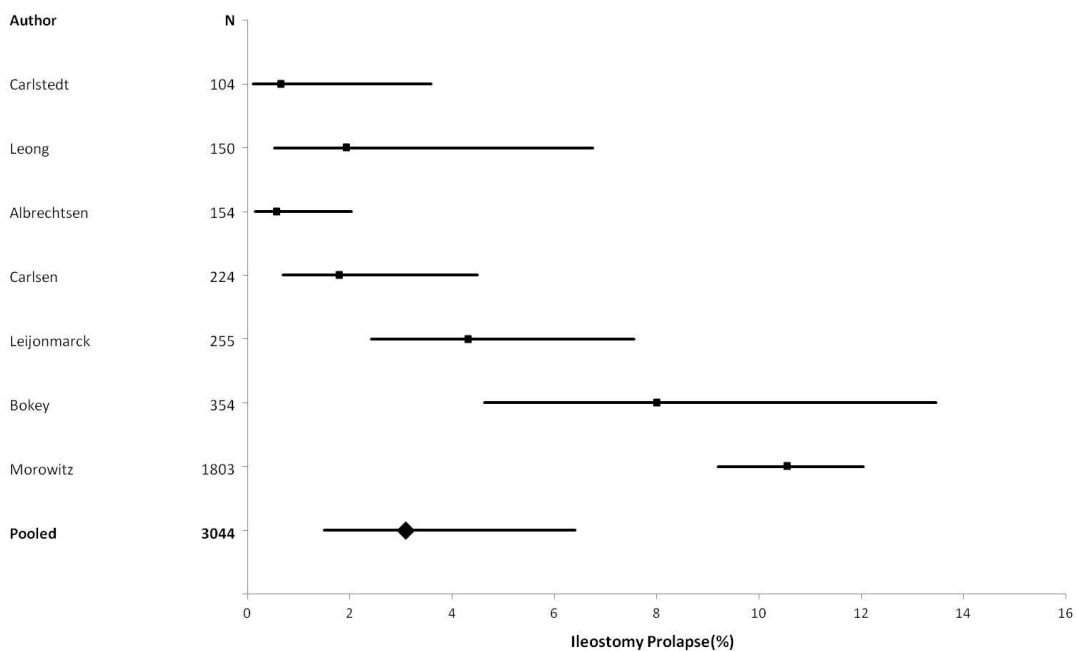
Figure 5.9 Forrest plot of studies reporting on rates of ileostomy fistula. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
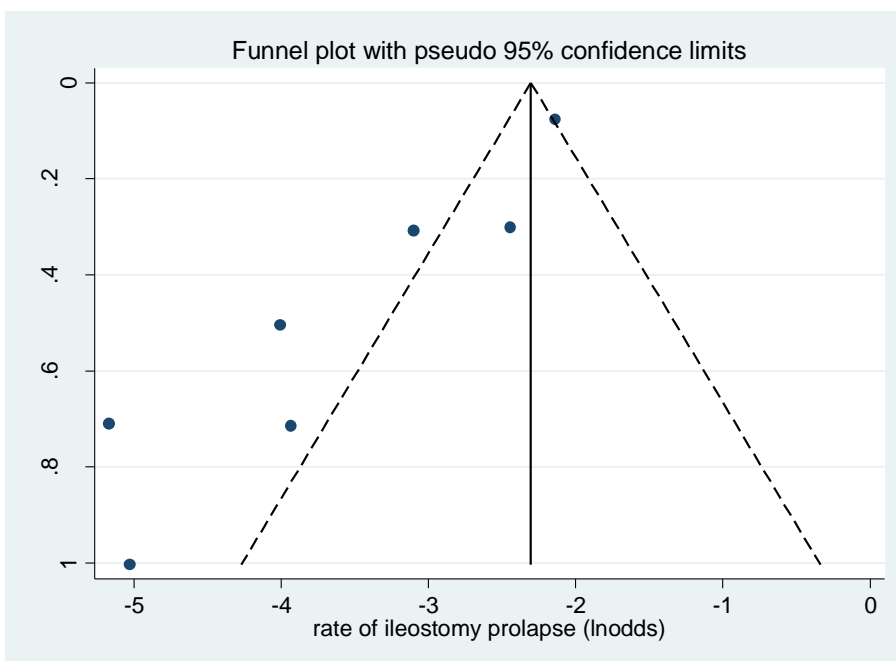

Figure 5.10 Funnel plot showing rate of ileostomy fistula (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of ileostomy fistula.

Parastomal Hernia

Seven studies totalling 3,005 patients reported on the rate of parastomal hernia requiring repair, with individual study estimates ranging from 0.9% to 10.0% [11-13, 15, 17-19]. The pooled estimate was 3.5% (95% CI, 2.0%-6.1%) with significant heterogeneity p = <0.001, I^2 at 80.8% (Table 5.3). Figure 5.11 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of parastomal hernia within that study was 6.3%. Limiting the studies to ones that only reported on patients with ulcerative colitis resulted in a pooled rate of parastomal hernia of 4.1% (95%CI, 2.1%-7.9%) for 3 studies reporting on a total of 2,162 patients. A funnel plot (Figure 5.12) shows evidence of publication bias with fewer smaller studies being published with higher rates of parastomal hernia.
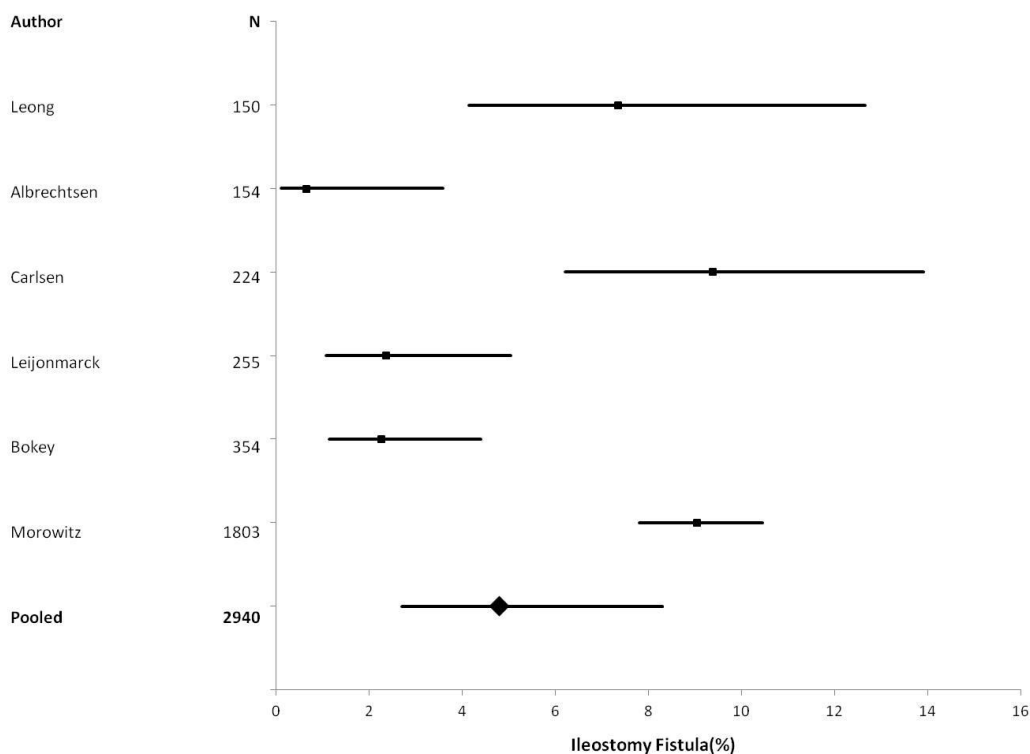
Figure 5.11 Forrest plot of studies reporting on rates of parastomal hernia. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
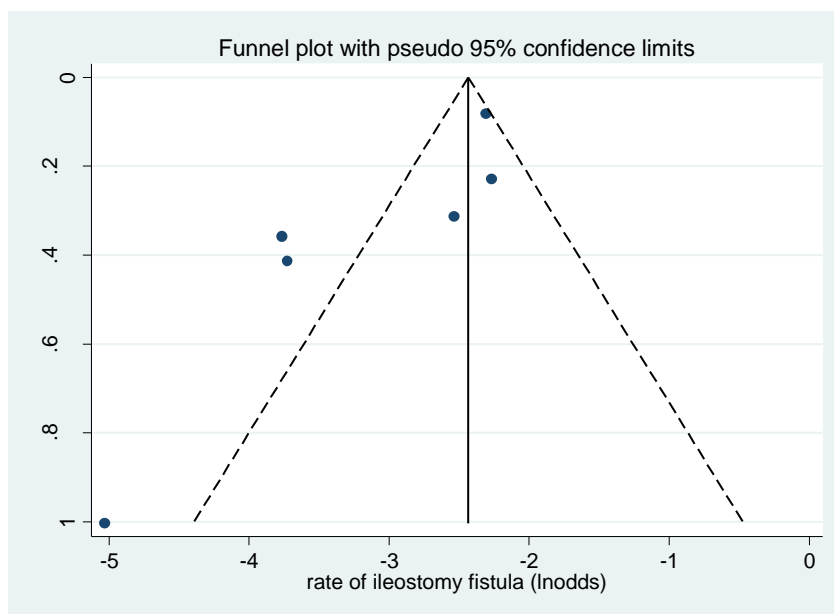

Figure 5.12 Funnel plot showing rate of parastomal hernia (ln(odds)) against study standard size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of parastomal hernia

Small Bowel Obstruction

Seven studies totalling 2,849 patients reported on the rate of small bowel obstruction requiring operation, with individual study estimates ranging from 1.8% to 18.0% [11-13, 15, 17, 19, 20]. The pooled estimate was 9.1% (95% CI, 6.5%-12.8%) with significant heterogeneity p = <0.001, I^2 at 78.5% (Table 5.3). Figure 5.13 graphically summarizes each study estimate, 95% confidence interval, and pooled estimate. Looking at the largest study, the questionnaire of 1,803 patients, the rate of small bowel obstruction requiring operation within that study was 12.7%. Limiting the studies to ones that only reported on patients with ulcerative colitis resulted in a pooled rate of small bowel obstruction of 7.7% (95%CI, 3.8%-15.3%) for 3 studies reporting on a total of 2,116 patients. A funnel plot (Figure 5.14) shows evidence of publication bias with fewer smaller studies being published with higher rates of small bowel obstruction.
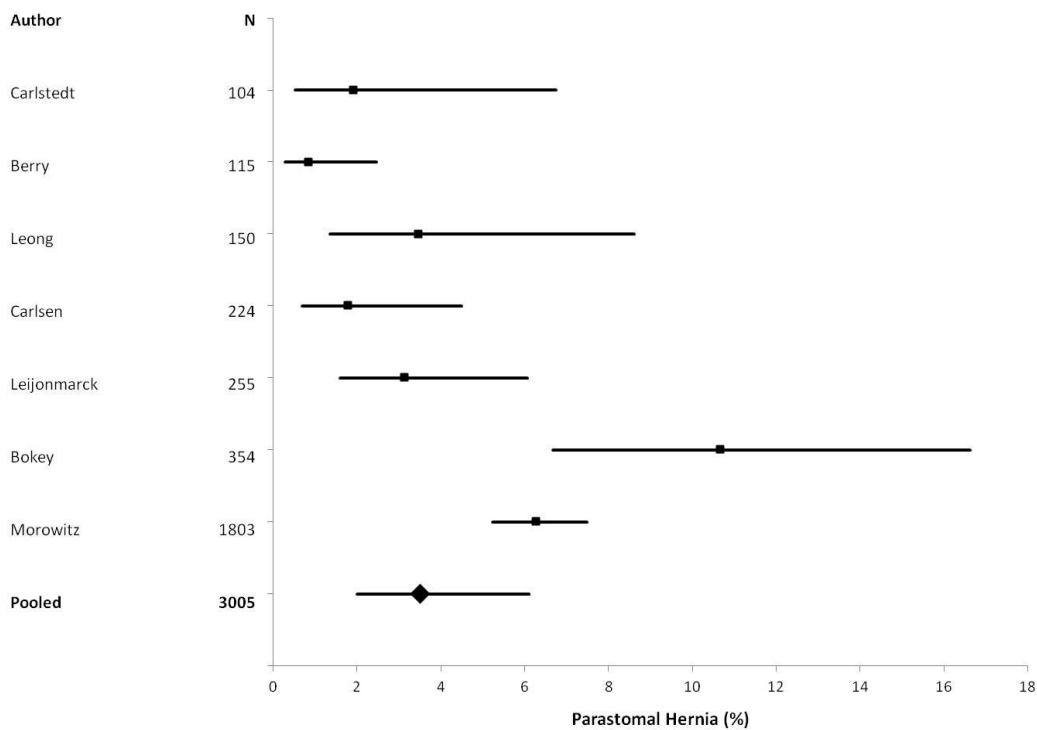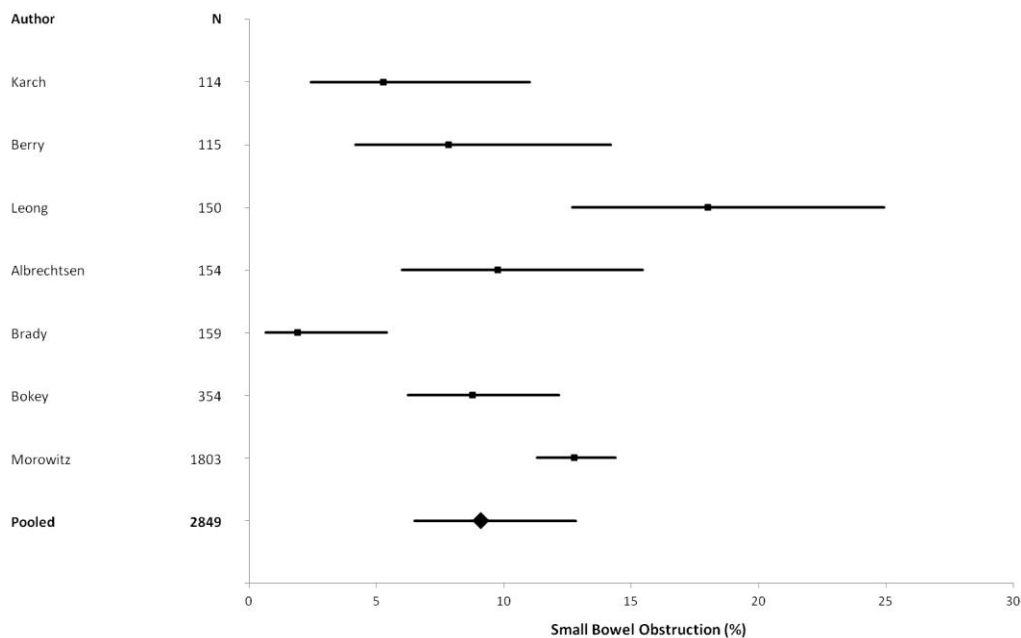
Figure 5.13 Forrest plot of studies reporting on rates of small bowel obstruction. Point estimates are provided along with 95% confidence intervals for each study and the pooled estimate. Studies are arranged in increasing order of size.
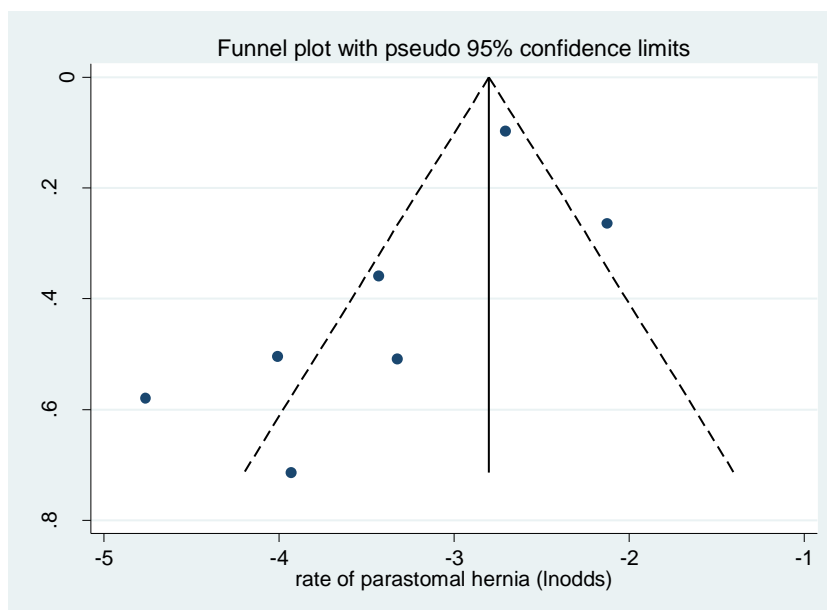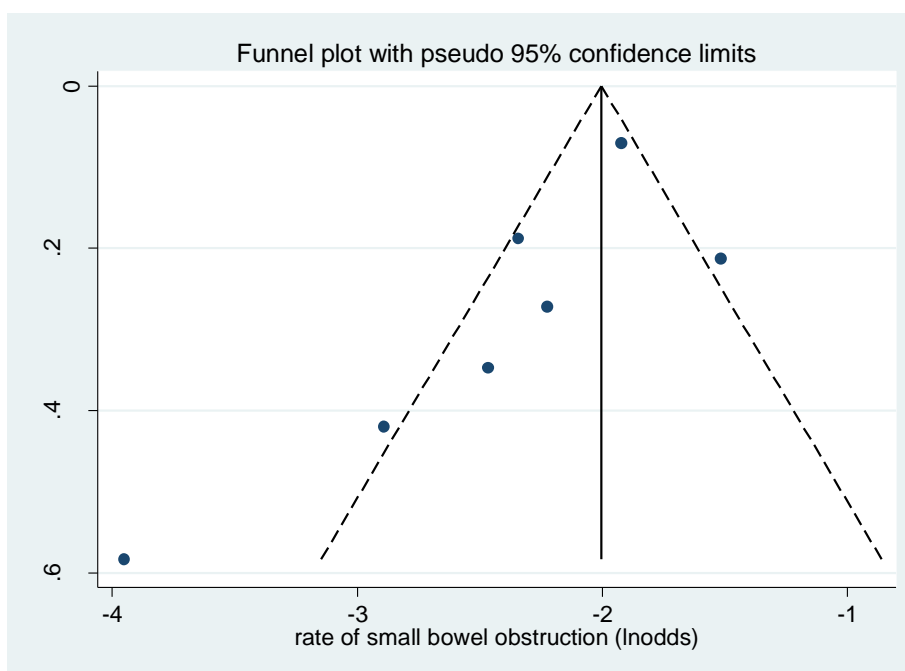

Figure 5.14 Funnel plot showing rate of small bowel obstruction (ln(odds)) against study size. Lack of studies in bottom right hand corner indicates a lack of small studies being published with higher rates of small bowel obstruction

Table 5.3 Results of Meta-Analysis of Complications Following Colectomy and Ileostomy

Complication (ileostomy)	Number of Studies	Number of Patients	Pooled %	95% CI	Heterogeneity I^2(%)	p
Revision						
Total	10	3,432	17.1	13.1-22.1	86.4	<0.001
UC only	5	2,475	14.5	9.1-22.2	86.2	<0.001
Stenosis						
Total	7	3,044	5.7	3.5-9.5	85.5	<0.001
UC only	4	2,316	7.3	3.9-13.3	86.6	<0.001
Retraction						
Total	6	2,894	6.2	2.7-13.3	95.0	<0.001
UC only	4	2,316	11.3	6.1-20.1	91.4	<0.001
Prolapse	7	3,044	3.1	1.5-6.4	88.4	<0.001
Total	7	3,044	3.1	1.5-6.4	88.4	<0.001
UC only	4	2,316	3.6	1.4-9.8	86.9	<0.001
Fistula						
Total	6	2,940	4.8	2.7-8.3	85.0	<0.001
UC only	3	2,212	3.1	0.8-8.3	84.2	<0.001
Parastomal hernia						
Total	7	3,005	3.5	2.0-6.1	80.8	<0.001
UC only	3	2,162	4.1	2.1-7.9	69.1	0.04
Small Bowel Obstruction						
Total	7	2,849	9.1	6.5-12.8	78.5	<0.001
UC only	3	2,116	7.7	3.8-15.3	78.3	0.003

5.3 Discussion

Although technically simple when compared to reconstructive procedures, proctocolectomy and ileostomy can also lead to significant long-term complications related to the presence of the ileostomy. Ileostomy revision can be one of the most severe problems as patients must have the ileostomy re-fashioned either at the same site or at an entirely new site. The pooled rate of ileostomy revision for all studies was 17.1%, and among studies limited to patients with ulcerative colitis, the rate was slightly lower at 14.5%. Of those studies that listed them, the most common indications for revision were stenosis[16, 19], retraction[11, 18], or obstruction at the ileostomy site[13]. Ileostomy revision can occur locally or can necessitate a full laparotomy with re-siting of the stoma to another area of the abdominal wall. The rate of local-only repair varied between those studies that reported it from 28% to83%[16, 19]. Patients with Crohn's disease have a higher rate of ileostomy revision when compared to ulcerative colitis. Carlsen et al reported the need for ileostomy revision among Crohn's patients was 59.3% versus 18.6% among those with ulcerative colitis[19]. Similarly, in the only prospective study, Carlstedt et al identified the need for revision among patients with Crohn's disease was 44% versus 24% among ulcerative colitis patients[16].

The rate of peristomal fistula has also been found to be higher among patients with Crohn's disease[16, 19]. This was reflected by the lower rate of peristomal fistula when our meta-analysis was restricted to those studies reporting solely on patients with ulcerative colitis, 3.1% versus 4.8%. Interestingly, the rates of other stoma-related complications were higher in the ulcerative colitis subgroup when compared to Crohn's disease (Table 5.3). Given that many comparative studies have shown that Crohn's

patients are at higher risk of stoma-related complications, this likely results from differences in study design or characteristics relating to length of follow-up, outcome definition, losses to follow-up, and other study-level factors. Given these differences in outcome rates identified in the meta-analysis, we will limit the use of pooled outcomes from studies solely reporting on patients with ulcerative colitis for inclusion in the decision aid.

Like patients with restorative procedures, patients who have undergone a proctocolectomy and ileostomy are at significant risk of small bowel obstructions requiring operative therapy. The pooled estimate among studies solely reporting on ulcerative colitis patients was 7.7%. Looking at the study with the longest reported follow-up, the rate of small bowel obstruction was 18%[17]. This underscores the ongoing risk for small bowel obstruction that carries on beyond the immediate post-operative period. Length of follow-up likely plays a role in explaining the different rates of stoma-related complications, although it was not possible to examine this as only three studies reported on the length of follow-up.

Only one study reported on the most common problem faced by ileostomates, that of skin irritation. In Morowitz's patients questionnaire, 1005 of 1803 (55.7%) patients complained of significant skin irritation[11]. Although this rarely leads to ileostomy revision, this complication can be distressing to patients and must also be considered by those contemplating life with an ileostomy.

Although proctocolectomy and ileostomy is considered the benchmark to which all other procedures for the treatment of ulcerative colitis are to be compared with[22, 23], there is a lack of methodologically sound studies reporting on the complications of this

procedure. The quality of the studies reporting on outcomes following proctocolectomy and ileostomy are even poorer than those presented in the preceding chapter of studies reporting on IPAA. Only three of the studies reported on length of follow-up, only one of seven studies was prospective, and very few defined any of their outcomes. In addition, many of the studies reported on patients that were operated on in the 1950s and 1960s, with less advanced peri-operative care than the modern era. This is important to consider as the outcomes reported here will be included in a decision aid and compared to ones from restorative procedures which were carried out during the 1980s -2000s. Given the large number of patients who choose to undergo restorative procedures, it may be difficult to obtain large numbers of patients who have had the conventional treatment of proctocolectomy and ileostomy. In a study of over 25,000 ulcerative colitis patients of whom 215 had a colectomy, only 29 patients had a total proctocolectomy and end-ileostomy[24]. This discrepancy in number of patients makes it difficult to compare the results of ileostomy to those of IPAA. As was seen in the preceding chapter, there exists a wealth of studies reporting on the results of IPAA, while only 11 studies were identified that reported on the results of colectomy and ileostomy. This discrepancy is further compounded by the very poor quality of the ileostomy studies. Each outcome reported in the meta-analysis contained significant heterogeneity (Table 5.3). Unlike the IPAA literature, there were too few studies to carry out any meta-regression or any meaningful subgroup analyses to explore this heterogeneity.

Although severely limited by the small number of studies, historical nature of patient cohorts, and poor study quality, we show that patients with ulcerative colitis who undergo a total proctocolectomy and end-ileostomy do have a significant risk of

ileostomy revision with a pooled estimate of 14.5% (95% CI, 9.1%-22.2%). Most other

stoma-related complications occur relatively infrequently (<10%); and patients are at risk

of requiring surgery for a bowel obstruction in the future, as high as 18% among studies

with longer follow-up. The risks of these potential complications along with the obvious

changes in body image, daily routine, and lifestyle must be considered by patients who

are deciding between IPAA and ileostomy.

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CHAPTER SIX- REFINEMENT AND TESTING OF PROTOTYPE DECISION AID

6.0 Introduction

A patient's decision between treatment options is complex and requires the assimilation of a large volume of information regarding complications and expected outcomes. It is imperative that patients select the surgical procedure that best fits with their own expectations and values. There is a paucity of data concerning effective communication methods for patients with IBD[1]. Despite a paucity of data, patients with ulcerative colitis who require surgery are faced with deciding between a restorative pouch procedure or an ileostomy. Decision aids are tools designed to facilitate communication of information to patients and enhance their ability to exercise treatment preferences[2, 3].

At least 55 randomized controlled trials have evaluated different decision aids for various medical decisions[4]. These trials have generally found the use of decision aids to lead to improved patient knowledge, reduced decision conflict, and improved patient satisfaction with treatment decisions, when compared with traditional methods of patient-physician interaction[4]. To our knowledge, no decision aids exist to assist patients with ulcerative colitis in making this difficult surgical decision. Our objective is to develop and evaluate a decision aid for patients with ulcerative colitis who are undergoing an elective proctocolectomy to help them decide between IPAA and ileostomy. The general aspects concerning both decision aids and ulcerative colitis and the role of surgery were discussed in chapter one of this work. Surgery is generally reserved for patients who fail medical management or who develop complications of ulcerative colitis (toxic colitis, perforation, cancer or dysplasia). Two main options exist for the patient following removal of the colon, either an ileostomy, where bowel movements are expressed into a

bag worn on the skin of the abdomen, or formation of a neo-rectum by using the small bowel as a pouch, known as ileal pouch-anal anastomosis (IPAA). Both options have been shown to have equivalent quality of life as demonstrated by the systematic review of these studies in Chapter Three. Despite equivalent quality of life, both options vary greatly in their procedure, changes to daily life, and complication profiles. Two separate systematic reviews and meta-analyses where conducted of studies reporting on complications following either procedure (Chapter 4-IPAA studies, Chapter 5- ileostomy studies), the results of which were used to construct a prototype decision aid. This pilot aid will then be refined by input from surgeons, enterostomal therapists, and patients. Following the refinement process, the aid will be tested for reliability and validity on healthy volunteers before being used with patients. This chapter describes the methodology behind this process and guides future endeavours aimed at further refinement of the aid.

6.1. Methods

To develop the decision aid we used accepted methodology[5-7] and followed quality criteria established by an international committee on patient decision aids[8]. The major steps involved in the development of this aid consist of gathering information, initial decision aid prototype construction and refinement, and evaluation of the decision aid on healthy volunteers for reliability and validity. Figure 6.1 outlines the major steps in the development.

6.1.1 Information sources

In order to determine what information to include in the decision aid we conducted a systematic review of the literature for studies of proctocolectomy and either ileostomy or IPAA. We have constructed a rough prototype based on the information retrieved from the systematic review and plan on presenting this to colorectal surgeons and enterostomal therapists to collect their input, and refine the prototype based on their recommendations. Finally, we will present the aid to patients with ulcerative colitis who have undergone either surgical option to identify information they feel is important in reaching a decision and to further refine our prototype.

6.1.2 Systematic Review and Prototype Design

Chapters Four and Five detail the methods and results of the systematic reviews of studies reporting on outcomes following either the IPAA option or the ileostomy option. Given the between study heterogeneity, we selected specific sub-groups of studies to include as a source of information for the aid. For the studies summarizing the results following ileostomy, we limited the inclusion of the pooled estimates from those studies that only reported on patients with ulcerative colitis, as we are dealing with this group of patients. For the IPAA studies, we systematically explored both clinical and methodologic study level factors for their influence on each outcome by using meta-regression methods. Those with a significant association and a clinical rationale (for example longer follow-up associated with higher rates of pouch failure) were used as the subgroup of studies for inclusion into the decision aid. The following table lists the point estimates used in the construction of the aid and the specific subgroup used as the source. For each point estimate generated from the literature, we expressed it as x/100 for all

outcomes. Utilizing a ratio with a common denominator is recommended by the International Patient Decision Aid Standards Collaboration as a way to present probabilities[8]. Along with a text-based description of the probabilities, we utilized a pictorial representation of the risk of complications. The addition of visual representations of risk have been shown to improve how easily and accurately patients process quantitative information[9]. In addition, the format of the visual information appears to affect the process with horizontally oriented pictographs being superior to vertical formats and pie charts[9, 10].

Table 6.1 Data Sources Used for Construction of the Decision Aid**.**

Intervention	Outcome	Point estimate	Subgroup
Ileostomy	Ileostomy revision	14.5% ~ 15/100	Ulcerative colitis
Ileostomy	Ileostomy stenosis	7.3% ~ 7/100	Ulcerative colitis
Ileostomy	Ileostomy retraction	11.3 ~ 11/100	Ulcerative colitis
Ileostomy	Ileostomy fistula	3.1 ~ 3/100	Ulcerative colitis
Ileostomy	Parastomal hernia requiring repair	4.1 ~ 4/10044	Ulcerative colitis
Ileostomy	Small bowel obstruction	7.7 ~ 8/100	Ulcerative colitis
IPAA	Pouch failure	6.1 ~ 6/100	Follow-up >5years
IPAA	Pelvic sepsis	11.4 ~ 11/100	Prospective studies
IPAA	Pouch fistula	9.4% ~ 9/100	Defined outcome criteria
IPAA	Anastomotic stricture	12.6 ~ 13/100	Defined outcome criteria
IPAA	Pouchitis	28.7% ~ 29/100	Defined outcome criteria/ follow-up >5 yrs
IPAA	Small bowel obstruction	22.5% ~23/100	Defined outcome criteria

IPAA	Sexual dysfunction	4.6% ~5/100	Overall group
IPAA	Fecal incontinence	9.1% ~ 9/100	≥ 85% J-pouch
IPAA	Fecal urgency	3.9% ~4/100	≥ 85% J-pouch
IPAA	Daily pad use	5.7% ~ 6/100	≥ 85% J-pouch
IPAA	Anti-diarrheal medication use	32.9% ~ 33/100	Overall group
IPAA	Number of BM/day	6.1 ~ 6 / day	≥ 85% J-pouch
IPAA	Number of BM/ night	1.0 ~ 1/night	Overall group

We constructed the prototype aid along three categories: information about the procedure, potential complications, and changes to daily life. This was constructed as an interactive power point presentation that is designed to be used by the surgeon with the patient during the clinical encounter. This can easily be modified and adapted into a pamphlet or be uploaded to the internet for patient self-study. We selected this format as the aid is not meant to replace the surgeon-patient interaction, but rather enhance the process of information exchange[11], and the International Patient Decision Aid Standards Collaboration do support the use of the aid in a guiding or coaching role during the patient-physician encounter[8]. In addition to presenting information about the procedures, specific values-clarification exercises have been built into the aid. The concept of values refers to the qualities that a given patient considers desirable or important, and the process of value clarification has become part of decision aids[4]. In the most recent systematic review, decision aids incorporating value clarification exercises were found to be more effective than simpler aids by improving patients' decisions and making them more congruent with their values[12].

Not all authors agree that value clarification has a role in decision aids. Nelson et al question whether patients need explicit value clarification, and point out that intuitive decision

making on the part of the patient may lead to better decisions as too much introspection and

attention to detail may disrupt intuitive processes and interfere with a patient's ability to focus on

the relevant material, or inhibit the formation of global impressions leading to a decision being

made[13]. Despite these theoretical concerns, we opted to include a short segment on value

clarification, as the recent literature has shown it to be effective in improving the decision making

process. To help clarify a patient's values, we listed a group of questions regarding various

attributes of each procedure and asked patients to indicate on a Likert scale how important each

attribute was to them, with a suggestion at each end of the spectrum corresponding to the

appropriate treatment option that fit with the value being expressed by the question. For example:

How important is it to you to avoid a stoma/ ileostomy?

Not important					Very Important
0	1	2	3	4	5
You should consider ileostomy			You should consider pouch		

Throughout our literature review we did not identify any studies that directly compared

survival between the two surgical options. Although it is not known with certainty, the survival

following each option is likely to be similar given the same control of disease. Thus we have

chosen to focus on highlighting the procedure-specific complications with our decision aid, in an

effort to help patients understand the difference between the two procedures. The prototype aid

can be found in Appendix B.

6.1.3 Input from Surgeons and Enterostomal therapists

Now that a rough prototype has been developed, we will present it to a group of three colorectal surgeons and two enterostomal therapists to obtain their feedback on the content, format, layout, and practical aspects of the prototype. We will also ask them to describe any information they feel is important to the patient interaction that we have omitted from the aid. The prototype will then be refined using this feedback. The interview guide for this focus group is included in Appendix C.

6.1.4 Input from Patients

We will conduct focus groups with patients who have had a proctocolectomy for ulcerative colitis. The goal of these groups is to identify information helpful to patients deciding between treatment options. In order to generate as much information as possible, we will use maximum variation sampling[20] by including patients that have had both surgical options, and patients that did and did not have complications following surgery. We will present the prototype to two groups, one of patients who underwent ileostomy and one of patients who underwent restorative proctocolectomy. Similar to our interaction with surgeons, we will seek feedback on the content, format, layout, and practical aspects of the aid. We will ask patients to describe any information they feel is relevant to the decision that we have omitted. Based on the information received from the patients we will modify the prototype further to incorporate their suggestions. This prototype will then be piloted on three patients who have recently undergone a proctocolectomy to further refine the aid for clarity and practicality. These patients will be recruited by their surgeon. The interview guide is included in Appendix D.

6.1.5 Reliability and Validity Testing

Once we have a refined prototype we will evaluate it in healthy volunteers for reliability and validity according to previously published methodology[5, 14, 1521,22]. We have decided to use volunteers rather than patients because it is clinically inappropriate and potentially unethical to manipulate information concerning therapy and outcomes to patients at the decision point[21,22]. An

interviewer will administer the instrument to 30 volunteers who will then state a preference between the two surgical options. In order to establish reliability we will re-administer the instrument 2 weeks later to the same volunteers and ask them to state their treatment preferences again. Reliability between treatment preferences will be measured using a kappa statistic. To establish validity we will change the information provided in the decision aid and determine if the volunteers' treatment choices change in a predictable manner based on the change in information present on the decision aid. For example, if a volunteer prefers the IPAA treatment option we will change the information to reflect an increase in pouch failure and see if manipulating the information present in the aid can result in a predictable change in decision. Volunteers will be recruited by use of posters put up at both the UWO campus, and in University and Victoria Hospitals. The datasheet used for this portion of the project is included in Appendix E. University ethics approval form for this portion of the project is included in Appendix F.

Systematic review and data abstraction

↓

Creation of rough prototype

↓

Presentation of prototype to surgeons and enterostomal therapists

↓

Presentation of refined prototype to two groups of patients (ileostomy group and restorative proctocolectomy group)

↓

Piloting of Aid to patients who have undergone the decision for clarity

↓

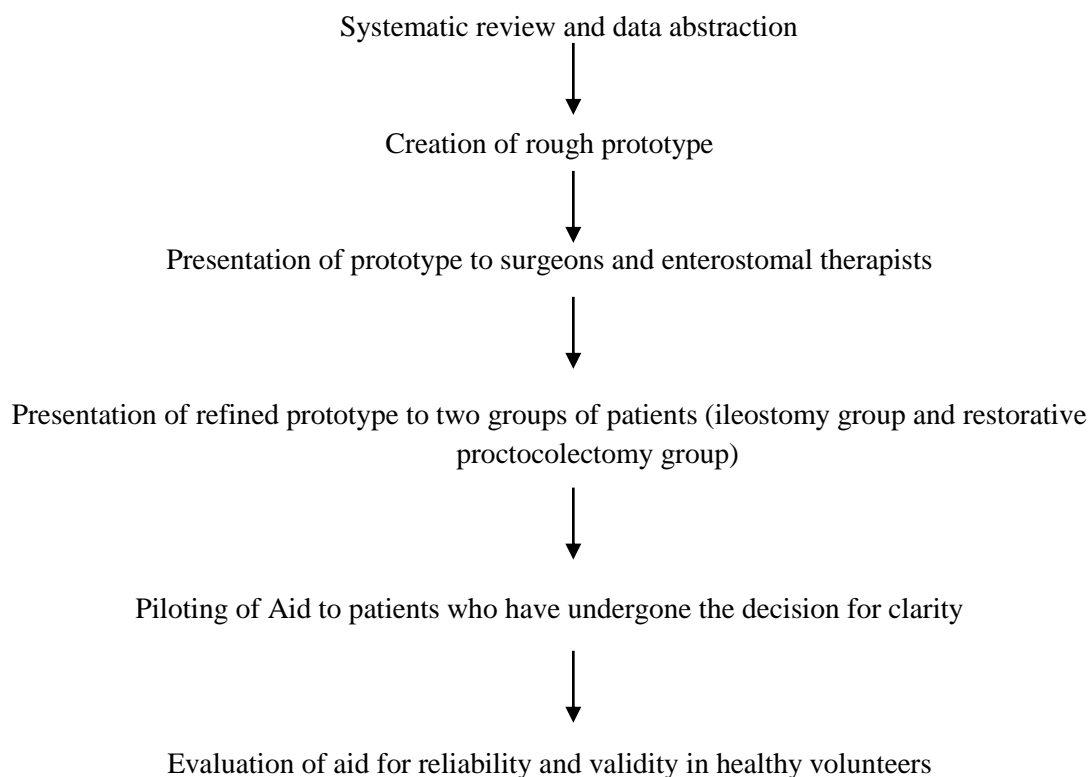Evaluation of aid for reliability and validity in healthy volunteers

Figure 6.1 Flow Chart Outlining Steps in the Development of the Decision Aid.

6.2 Conclusions and Further Directions

This work outlines the steps necessary in the design of a decision aid to help patients with ulcerative colitis decide between ileostomy and IPAA procedures. Although limited by the poor quality and heterogeneous literature, we used a systematic and rigorous process of exploring heterogeneity amongst the IPAA studies in order to select the most appropriate subgroup of studies to include in the aid. With a valid and reliable decision aid, the next step would be its evaluation on patients with ulcerative colitis. The aid will be administered to patients with ulcerative colitis who are at the decision point and following this several established outcomes for decision aids would be assessed including knowledge about the options and their complications, decisional conflict[16], risk perception[12, 17], preferred role in decision making[18], and satisfaction with decision making[19]. This evaluative process would necessitate a randomized controlled trial and the specific methodology is beyond the scope of this work, but is the next step in the evaluation of this decision aid.

There now exist a wealth of literature supporting the benefits of decision aids in enhancing the decision making process for patients. The decision between an ileostomy or a restorative pouch procedure is well suited to the use of a decision aid and with a rough proto-type now designed, further work will look towards refinement and evaluation of this aid with the hope of improving these patients decision making process.

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APPENDIX A- Search Strategies Used to Identify Primary Studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
----
1   exp Colitis/ or Colitis, Ulcerative/ or Inflammatory Bowel Diseases/
2   (inflammatory bowel disease$ or ulcerative colitis or IBD or colitis).mp.
3   1 or 2
4   Colonic Pouches/ or Proctocolectomy, Restorative/ or Ileostomy/
5   (j pouch$ or y pouch$ or w pouch$ or continent pouch$).mp.
6   (ileo pouch anal-anastomosis or ileo pouch anal anastomosis or IPAA or end-ileostomy or end ileostomy or ostom$ proctocolectom$ colectom$).mp.
7   4 or 5 or 6
8   3 and 7
9   limit 8 to yr="1978 -Current"
****

Database: Cochrane Library
Search Strategy:
----
1   ((ulcerative adj2 coliti$) or coliti$ or (inflammatory bowel adj2 disease$) or IBD or inflammatory bowel).mp.
2   (ileo pouch anal anastomosis or ileonalanastomosis or IPAA or anastomosis).mp.
3   (proctocolectom$ or end-ileostom$ or end ileostom$ or ileostom$ or ostomy).mp.
4   (colonic pouch$ or continent pouch$ or y pouch or w pouch or j pouch or ileoanal reservoir$ or anal reservoir$).mp.
5   2 or 3 or 4
6   1 and 5
7   limit 6 to yr="1978 -Current"

****

Database: Embase
Search Strategy:

----

1   exp Colitis/ or Enteritis/ or Ulcerative Colitis/
2   (inflammatory bowel disease$ or ulcerative colitis or IBD or colitis).mp. (77269)
3   1 or 2
4   ileoanal anastomosis/ or ileostomy/ or proctocolectomy/ or continent ileostomy/ or Colon Pouch/
5   colon pouch/ or rectum anastomosis/ or exp rectum resection/
6   (colon$ pouch$ or ileoanal anastomosis or proctocolectom$ or ileostom$ or colon pouch$ or ostomy).mp.
7   (j pouch$ or y pouch$ or w pouch$ or continent pouch$).mp.
8   4 or 5 or 6 or 7
9   3 and 8
10   limit 9 to yr="1978 -Current"
11   remove duplicates from 10

****

APPENDIX B-PROTOTYPE DECISION AID

Helping you deciding on your surgical option

Prototype decision aid for patients with ulcerative colitis deciding between end-ileostomy and IPAA

- Your surgeon has recommended surgery
- You require this for control of your ulcerative colitis

What are my options?

- 1 in 4 people with this disease will require removal of the colon and rectum because medications are no longer controlling their symptoms or they have developed colon cancer
- There are two surgical options to deal with this situation:
    - proctocolectomy and end-ileostomy
    - proctocolectomy and ileo-anal pouch
- For each treatment option we will discuss the procedure, the potential complications and the changes to your daily life
- Although not known with certainty, both treatments are thought to result in the same chance of survival

Click on a box for more information:

End-ileostomy

Description   Complications   Changes to Daily life

Ileo-anal-pouch

Description   Complications   Changes to Daily life

What is important to you ?

End-ileostomy

- Entire colon and rectum is removed
- Your small bowel is connected to your skin (called a stoma)
- You pass digested food into a bag connected to your skin
- Your anus is closed
- Done during one procedure
- You stay in hospital for approximately 5-7 days.

End-Ileostomy Complications

Complication	Risk	What to expect
Ileostomy revision	15 out of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to fix a problem with the ileostomy
Small bowel obstruction	8 out of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to fix a blockage in their bowels
Parastomal hernia	4 out of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will require surgery to repair a hernia around their ostomy

End-Ileostomy Complications

Complication	Risk	What to expect
Ileostomy retraction	11 of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to fix their stoma because it has sunken down into their belly
Ileostomy stenosis	7 of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to fix their stoma because it is too tight and narrow to allow passage of stool
Ileostomy fistula	3 of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will require surgery to repair an infection related to a connection between the stoma and the surrounding skin

End-Ileostomy
Changes to Daily life

- Most patients need to change the bag 3-4 times/ day, and replace the bag every 3-5 days
- Rarely do they need to change the bag at night
- Most patients with a stoma can participate in normal activities (swimming, sex)
- Most patients who have a stoma are satisfied with their life

Ileo-Anal Pouch

- Entire colon and rectum is removed
- The small bowel is connected to the anus and a new rectum is formed from this small bowel (pouch) so that digested food is past through the anus
- Usually requires two surgeries: one where the pouch is made and a temporary stoma is formed
- The stoma is then closed during a second surgery
- Requires at least two operations each with a 5-7 day hospital stay

Ileo-Anal Pouch Complications

Complication	Risk	What to expect
Pouch failure	6 of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to either remove their pouch or have a permanent stoma created and will no longer have bowel movements via their anus
Pouchitis	29 of 100 patients who undergo the procedure will develop this	These patients will develop irritation of their pouch causing pain, frequent bloody bowel movements, and the urge to pass feces with up to 20 bowel movements per day. This condition will usually respond to antibiotics but may become difficult to treat in 1/3 patients
Small bowel obstruction	23 of 100 patients who undergo the procedure will develop this	At some point in the future, these patients will need to have surgery to fix a blockage in their bowels

Ileo-Anal Pouch Complications		
Complication	**Risk**	**What to expect**
Pelvic Sepsis	11 of 100 patients who undergo the procedure will develop this	These patients will develop a severe infection in their abdomen following surgery that may require a stoma or a drain to treat
Pouch Fistula	9 of 100 patients who undergo the procedure will develop this	These patients will develop an infection related to a communication between the pouch and either the skin around the anus or vagina that may require a stoma to treat
Anastomotic stricture	13 of 100 patients who undergo this procedure will develop this	These patients will develop a narrowing at their anus that requires dilatation for treatment
Sexual dysfunction	5 of 100 patients who undergo this procedure will develop this	These patients will develop problems with their sexual functioning (inability to achieve an erection or pain and vaginal dryness during sex)

Ileo-Anal Pouch
Changes to Daily life

Change in bowel habit	Risk	What to expect
Number of bowel movements per day	Most patients will have on average 6 bowel movements per day	
Number of bowel movements per night	Most patients will have on average one bowel movement at night	
Fecal incontinence	9 of 100 patients who undergo the procedure will develop this	These patients will experience daily leakage of stool
Fecal urgency	4 of 100 patients who undergo procedure will develop this	These patients will experience an urge to defecate and will need to find a toilet immediately to pass feces
Daily pad use	6 of 100 patients who undergo this procedure will develop this	These patients will need to wear pads on a daily basis to protect their clothes from stool leakage

What is important to you ?

- Certain aspects of the surgeries may be more important to you and may help you decide between the two options

- The following questions may help you decide on a surgical option by presenting you with aspects of each treatment and asking you how important these are

How important is it to you to avoid a stoma/ ileostomy?					
Not Important					Very Important
0	1	2	3	4	5
Reason to consider ileostomy			Reason to consider pouch procedure		

How important is it to you to avoid a second procedure?					
Not Important					Very Important
0	1	2	3	4	5
Reason to consider pouch procedure			Reason to consider ileostomy		

How important is it to you to avoid a complication following the surgery?					
Not Important					Very Important
0	1	2	3	4	5
Reason to consider pouch procedure			Reason to consider ileostomy		

How important is it to you to avoid any risk of fecal incontinence?					
Not Important					Very Important
0	1	2	3	4	5
Reason to consider pouch procedure			Reason to consider ileostomy		

- Thank you for using the decision aid, we hope it was helpful in your decision making
- Do not hesitate to ask your surgeon to clarify any information presented here that you did not understand

APPENDIX C-Prototype-Refinement Phase I
Interview Guide
Group: Surgeons and Enterostomal Therapists

Moderator: Luc Dubois
Method: Focus Group
Goals:
1) Collect input from surgeons and enterostomal therapists on the content, format, and practical aspects of the decision aid.
2) Seek additional information surgeons or eneterostomal therapists find relevant to the decision.

Pre-amble
" I would like to thank everyone for agreeing to help with this research project. The goal of this project is to develop a decision aid that will help patients with ulcerative colitis choose between restorative proctocolectomy with ileal anal-pouch anastomosis or end-ileostomy. The purpose of this meeting is to discuss and comment on the decision aid we have constructed. We are seeking your input into the content, format, and practical aspects of the decision aid.

This discussion should take approximately one hour. We will record this discussion and analyse the recording to identify any recommendations and refinements for the decision aid.

Your answers will be kept confidential and your participation in this group is voluntary, you may leave or refuse to participate at any time.

Before we begin are there any questions about this project or the purpose of this meeting?
"

I Present the decision aid prototype to the group

II Seek input from surgeons and enterostomal therapists on the following domains:

1) Content
Framing question:
Do you have any comments on the content we have included in the aid?

Follow-up questions:

Do you think the information about the procedure, benefits, functional outcomes, and risks accurate?

Would you be comfortable presenting this information to your patients?

Is there any further information you would recommend we include in the aid that we have not presented?

Is the language of an appropriate level for your patients?

Should we include graphical representations or pictures of certain aspects of the procedure?

Is there any information you don't understand or think patients would have difficulty understanding?

Are there any changes you would make to the content of the aid?

2) Format

Framing question:
Do you have any comments about the format of the aid?

Follow-up questions:
Do you think the current format facilitates discussion with patients?

Are there any other formats (board, pamphlet) that you would prefer for the aid?

Are there any changes you would make to the format?

3) Practical Aspects

Framing question:
Do you have any concerns about the practical aspects of the aid?

Follow-up questions:
In your opinion, how long should the aid take to administer?

Are there any elements of the aid you think would hamper patient interaction?

Are there any elements that we have omitted that would aid patient interaction?

Are there any changes you would make to the aid to improve its practicality?

4) Overall Impression:

Know that you have considered all aspects of the aid, are there any further changes you would recommend we make?

III Closing Remarks

"Are there any remaining questions or comments? The audio recording will be analyzed and the aid will be modified according to your feedback. A modified version of the aid will be sent to you once the changes are made. Thank you again for participating in our research project."

Prototype-Refinement Phase I
Data Sheet Group: Surgeons and Enterostomal Therapists
Date of focus group:

Participant Characteristics

Surgeon	Age	Sex	Years in Practice
1			
2			
3			

Enterostomal Therapists	Age	Sex	Years in Practice
1			
2			
3			

Results of Group Discussion

Comments	Changes Proposed

APPENDIX D Prototype-Refinement Phase II
Interview Guide
Group: Patients with ileal anal-pouch anastomosis
Moderator: Luc Dubois
Method: Focus Group
Goals:
1) Collect input from patients on the content, format, and practical aspects of the decision aid.
2) Seek additional information patients find relevant to the decision.

I Pre-amble

" I would like to thank everyone for agreeing to help with this research project. The goal of this project is to develop a decision aid to assist patients with ulcerative colitis when deciding between two surgical options. One is to remove the colon and make a new rectum from the small bowel (ileal anal-pouch anastomosis), the other is to bring the small bowel out to the skin as an ileostomy. The purpose of this meeting is to discuss and comment on the decision aid we have constructed. We are seeking your input into the content, format, and practical aspects of the decision aid."

"This discussion should take approximately one hour. We will record this discussion and analyse the recording to identify any recommendations and refinements for the decision aid."

"Your answers will be kept confidential and your participation in this group is voluntary, you may leave or refuse to participate at any time."

"We recognize that discussing aspects of your prior treatment and illness may be upsetting, if you feel you need to leave at any moment, please feel free to do so. If you feel you require any counselling or other help following this meeting, we will work with you to arrange it."

"Keep in mind that there are no right or wrong answers to these questions."

"Before we begin are there any questions about this project or the purpose of this meeting? "

II Present the decision aid prototype to the group

III Seek input from patients on the following domains:

1) Content
Framing question:
 Do you have any comments on the content we have included in the aid?

Follow-up questions:

Is the information we have presented in the aid easy to understand?

Would the information in the aid be helpful in making a treatment decision?

Is there any information you think we should add to the decision aid?

Are there any elements of the decision aid we need to clarify?

Would the use of pictures representing the procedures help?

Do you think there is too much information included in the aid?

Do you think there is too little information in the aid?

Is there any language used in the aid that you feel is threatening?

2) Format

Framing question:
Do you have any comments about the format of the aid?

Follow-up questions:
Do you think the current format facilitates discussion with a surgeon?

Are there any other formats (board, pamphlet) that you would prefer for the aid?

Are there any changes you would make to the format?

Do you think a take-home version of the aid would be beneficial?

3) Practical Aspects

Framing question:
Do you have any concerns about the practical aspects of the aid?

Follow-up questions:
In your opinion, how long do you think it should take you to go through the aid?

Do you think any parts of the aid will prevent discussion with the surgeon?

Is the current layout easy to use?

Is the current layout inviting?

Would you recommend any changes to the layout or any other aspects of the aid?

4) Overall Impression:

Know that you have considered all aspects of the aid, are there any further changes you would recommend we make?

IV Closing Remarks

"Are there any remaining questions or comments? The audio recording will be analyzed and the aid will be modified according to your feedback. Thank you again for participating in our research project. If you have any residual questions please feel free to contact me."

Prototype-Refinement Phase II
Data Sheet
Group: Patients with ileal anal-pouch anastomosis

Date of focus group:

Participant Characteristics

Patients	Age	Sex	Years Since Surgery
1			
2			
3			
4			
5			
6			
7			
8			

Results of Group Discussion

Comments	Changes Proposed

Appendix E- Reliability and Validity Testing
Data Sheet-Page 1

| Participant Number ___ ___ | Date: __ __ __ __-__ __-__ __ |

Demographic Information	
1.Age (years)	_____
2.Gender	□ Male □ Female
3.Relationship Status	□ Married/ Cohabitating □ Single/ divorced/ widowed
4.Education	□ High School or equivalent or less □ College or University (post-secondary)

Decision Information: First Encounter	
Time of administration (mins)	_____
Decision with normal probabilities	□ End-ileostomy □ Ileal anal-pouch anastomosis
Decision with altered probabilities (validity)	□ End-ileostomy □ Ileal anal-pouch anastomosis
How easy was it to understand the information presented in the aid?	□ Very Easy □ Somewhat Easy □ Somewhat Difficult □ Very Difficult
How helpful was the decision aid in assisting you when making the decision?	□ Very Helpful □ Somewhat Helpful □ Somewhat Unhelpful □ Very Unhelpful
Decision Information: Second Encounter (reliability)	
Date of Second Encounter	__ __ __ __-__ __-__ __
Decision with repeated administration	□ End-ileostomy □ Ileal anal-pouch anastomosis

APPENDIX F- REB APPROVAL FORM

Research
Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Richard Malthaner
Review Number: 15837E
Review Level: Delegated
Approved Local Adult Participants: 60
Approved Local Minor Participants: 0
Protocol Title: Permanent ileostomy or ileo-anal reconstruction? Development of a decision aid for patients with ulcerative colitis undergoing an elective proctocolectomy
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics, London Health Sciences Centre
Sponsor:
Ethics Approval Date: March 22, 2012　　　　　　　　**Expiry Date:** December 31, 2013
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Study End Date	The study end date has been extended to December 31, 2013 as the project has not yet started.	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Janice Sutherland (jsutherl@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Shantel Walcott (swalcot@uwo.ca)

This is an official document. Please retain the original in your files.

Luc Dubois, M.D., F.R.C.S.(C.)

CURRICULUM VITAE

Academic Background and Training:

1. **Vascular Surgery Fellowship,** University of Western Ontario, London ON.
   2011-present

2. **Master's of Clinical Epidemiology**, University of Western Ontario, London ON.
   Candidate 2007-present

3. **Clinical Investigators Program**, University of Western Ontario, London ON.
   Candidate, 2007-present

4. **General Surgery Residency**, University of Western Ontario, London ON.
   2005- 2011

5. **Doctor of Medicine**, University of Western Ontario, London ON.
   2001-2005

6. **Bachelor of Science** with Honours in Biology and Minor in History, Mount
   Allison University, Sackville NB
   1996-2001

Journal Publications:

Published:

1. **Dubois L,** Durant C, Harrington DM, Forbes TL, DeRose G, Harris JR. Technical
   factors are strongest predictors of postoperative renal dysfunction following open
   juxtarenal abdominal aortic aneurysm repair. *The Journal of Vascular Surgery
   (accepted-Sept 2012).*

2. Vogt KN**,** Van Koughnett JA, **Dubois L**, Gray DK, Parry NG. The use of trauma
   transfusion pathways for blood component transfusion in the civilian population:
   A systematic review and meta-analysis. *Transfusion Medicine (accepted-2012)*

3. Racz J, **Dubois L,** Katchy A, Wall WJ. Elective and emergency abdominal
   surgery in patients 90 yrs of age or older. *The Canadian Journal of Surgery
   (accepted- 2011)*

4. **Dubois L**, Leslie K, Parry N. FACTS Survey: <u>F</u>AST use <u>A</u>mong <u>C</u>anadian Residents <u>T</u>raining in General <u>S</u>urgery. *The Journal of Trauma 2010;69(4):765-9.*

5. **Dubois L,** Vogt KM, Davies W, Schlachta CM. Impact of an outpatient appendectomy protocol on clinical outcomes and cost: A case-control study. *Journal of the American College of Surgeons 2010; 211(6):731-7.*

6. **Dubois L**, Gray DK. Splenectomy, does it still play a role in the management of thrombotic thrombocytopenic purpura? *The Canadian Journal of Surgery 2010;53(5):349-55.*

7. **Dubois L,** Malthaner RA. Video-assisted thoracoscopic bullectomy and talc poudrage for spontaneous pneumothoraces: effect on short term long function. *The Journal of Cardiovascular Surgery 2010; 140(6):1272-5.*

8. Karanicolas PJ, **Dubois L**, Colquhoun PH, Swallow CJ, Walter SD, Guyatt GH. The more the better? The impact of surgeon and hospital volume on in-hospital mortality following colorectal resection. *The Annals of Surgery 2009*; 249(6):954-9.

9. **Dubois, LA,** Gray DK, Tweedie EJ. Surgical images: soft tissue. Calcinosis cutis. *The Canadian Journal of Surgery 2007*; 50: 217-8

10. **Dubois LA**, Gray DK. Dopamine-secreting pheochromocytomas: In search of a syndrome. *World Journal of Surgery 2005*; 29:909-13

11. MacDonald TM, **Dubois L**, Smith LC, Campbell DA. Sensitivity of cyanobacterial antenna, reaction center and CO_2 assimilation transcripts and proteins to moderate UVB: light acclimation potentiates resistance to UVB. *Photochemistry and Photobiology 2003*; 77:405-12.

12. MacKenzie, TD, MaDonald TM**, Dubois LA**, Campbell DA. Seasonal changes in temperature and light drive acclimation of photosynthetic physiology and macromolecular content in *Lobaria pulmonaria*. *Planta 2001*; 214:57-66

Submitted:

1. **Dubois L**, Novick TV, Harris JR, DeRose G, Forbes TL. Outcomes following endovascular abdominal aortic aneurysm repair are equivalent between genders despite anatomic differences in women. *Submitted:* Journal of Vascular Surgery, August 2012.

2. Ahmadi N, **Dubois L,** McKenzie , Brown CJ, MacLean A, McLeod RS. Role of evidence based reviews in surgery in teaching critical appraisal skills and journal clubs. *Submitted:* Canadian Journal of Surgery, Feb 2012.

3. Vogt KN**, Dubois L**, Etemad-Rezi R, Schlachta CM. Diagnostic yield of imaging for patients presenting with suspected acute appendicitis. *Submitted:* Journal of the American College of Surgeons Jan 2012.

4. Vogt KN**, Dubois L**, Merritt N. Use of focused assessment with sonography for trauma (FAST) in North American pediatric trauma centres. *Submitted:* J Trauma, Nov 2011

Abstracts Presented (Presenter underlined):

1. <u>Vogt KN</u>, **Dubois L**, Vinden C. "Specialty bias" may help explain variable results of CT colonography in the literature. Poster at the *ASCRS Annual Scientific Meeting Vancouver BC May 2011*.

2. <u>Vogt KN</u>, Van Koughnett JA, **Dubois L**, Gray DK, Parry N. The use of trauma transfusion pathways for blood component transfusion in the civilian population: A systematic review and meta-analysis. Presented at the *ACS Region XII Resident Research Competition* Quebec City QC September 2010 **(Winner)**; Poster at the *Trauma Association of Canada Annual Scientific Meeting* Banff AB April 2011 **(Winner)**.

3. **<u>Dubois L</u>,** Vogt KM, Davies W, Schlachta CM. Impact of and outpatient appendectomy protocol on clinical outcomes and cost: A case-control study. *The Canadian Surgical Forum, Victoria, BC, 2009*

4. **<u>Dubois L</u>,** Leslie K, Parry N. FACTS Survey: <u>F</u>AST use <u>A</u>mong <u>C</u>anadian residents <u>T</u>raining in general <u>S</u>urgery. *The Canadian Surgical Forum: TAC/ACS Canadian Resident Papers Competition*, *Victoria, BC, 2009.*

5. <u>Racz JM</u>, **Dubois L**, Katchy A, Wall WJ. Elective and emergency abdominal surgery in patients 90 years of age or older- clinical outcomes and the evaluation of the POSSUM and P-POSSUM scoring systems as predictors of mortality. *The Canadian Surgical Forum, Victoria, BC, 2009.*

6. <u>Vogt KN</u>, **Dubois L**, Hobbs A, Etemad-Rezai, Schlachta CM. Diagnostic yield of imaging for patients presenting with suspected acute appendicitis. *The Canadian Surgical Forum, Victoria, BC, 2009.*

7. **<u>Dubois L</u>**, Karanicolas PJ, Colquhoun PHD, Guyatt GH. Short-term outcomes following colorectal resection for diverticular disease in Canada. *The Canadian Surgical Forum, Halifax, NS, 2008.*

8. <u>Karanicolas PJ</u>, Colquhoun PHD, **Dubois L**, Swallow CJ, Guyatt GH. An analysis of 1486 colorectal resections performed for inflammatory bowel disease in Canada. *The Canadian Surgical Forum, Halifax, NS, 2008.*

9. **<u>Dubois L</u>**, Malthaner RA. VATS apical bulectomy and talc poudrage in the treatment of spontaneous pneumothoraces: effect on pulmonary function and 1-year results.*18th World Congress-World Society of Cardio-Thoracic Surgeons, Kos Island, Greece, 2008.*

10.   **<u>Dubois L</u>**, Gray DK. Predictors of response to splenectomy in patients with immune thrombocytopenic purpura. *Resident Research Retreat, The Canadian Surgical Forum, Calgary, Alberta, 2006.*

11.   <u>Campbell DA</u>, MacDonald TM, **Dubois LA**, Comeau S, Smith S. Moderate UVB triggers dynamic regulation of cpc, psbA, rbcL transcripts in the cyanobacterium Synechococcus sp, PCC 7942. *12th International Photosynthesis Congress, Brisbane, Australia, 2001.*

12. <u>MacKenzie, TD</u>, MacDonald TM, **Dubois LA**, Campbell DA., Seasonal changes in temperature and light drive acclimation in a lichen. *12th International Photosynthesis Congress Brisbane, Australia, 2001.*

Research Grants:

1. Physician Services Incorporated Foundation Resident Research Grant, PSI Foundation. (August 2010). Project Title: The use of gentamicin-impregnated collaged implants to prevent surgical site infection in colorectal surgery. A randomized controlled trial. Principle Investigator: KN Vogt; Co-investigator and trial statistician: **L Dubois**. *($20 000)*

Awards and Distinctions:

1. **Department of Surgery Research Award for Best Resident Paper (Western):** For the paper entitled, *Technical Factors are Strongest Predictors of Postoperative Renal Dysfunction Following Open Juxtarenal Aneurysm Repair*, *2012*

2. **G. E. Meads Award:** For Excellence in technical ability and teaching in general surgery residency, *2011*.

3. **Stevens Norvell Award:** for the highest mark amongst all Canadian residents in general surgery on the annual Canadian Association of General Surgeons exam, *2011*.

4. **Stevens Norvell Award:** for the second highest mark of all Canadian PGY-4 residents in general surgery on the annual Canadian Association of General Surgeons exam, *2010.*

5. **Canadian Association of General Surgeons: Resident Award for Teaching Excellence**. *June 2010*.

6. **Best Research Poster Award:** Impact of and outpatient appendectomy protocol on clinical outcomes and cost: A case-control study. *The Canadian Surgical Forum, 2009.*

7. **Best Resident Research Paper from Ontario**: FACTS Survey: FAST use Among Canadian residents Training in general Surgery. *TAC/ACS Canadian Resident Papers, The Canadian Surgical Forum, 2009.*

8. **Stevens Norvell Award:** for the highest mark of all Canadian PGY-3 residents in general surgery on the annual Canadian Association of General Surgeons exam, *2008.*

9. **Schulich Graduate Scholarship for Medical Research**, *2007&2008.*

10. **Patterson Scholarship for Clinical Investigators Program**, *2008*.

11. **Stevens Norvell Award:** for the second highest mark of all Canadian PGY-1 residents in general surgery on the annual Canadian Association of General Surgeons exam, *2006.*

12. **Best First Year Research Paper:** Predictors of response to splenectomy in patients with immune thrombocytopenic purpura. *UWO General Surgery Annual Resident Research Day, 2006.*

13. **Dr. Fred N. Hagerman Memorial Prize in Surgery:** awarded to the graduating student in medicine showing the greatest merit in surgery, *2005*.

14. **Kingswood Scholarship:** awarded to the graduating student in medicine considered the most proficient by the authorities of the university, *2005*.

15. **Dr. C.C. Ross Memorial Prize in Surgery**: awarded to the student at the end of clinical clerkship showing the most proficiency in surgery, *2004*.

16. **John C. Rathbun Memorial Prize in Pediatrics:** awarded to the student who receives the highest evaluation at the completion of the clinical clerkship in pediatrics, *2004*.

17. **Rachel Slobasky Kaplan Scholarship:** awarded annually to the student achieving the highest standing in the examinations at the conclusion of year two of medicine, *2003*.

18. **J.A.F. Stevenson Award**: awarded annually to one medical student from any year on the basis of academic excellence in the previous year, *2003*.

19. **Meds Class of 1940 Scholarship in Medical Sciences:** awarded to the student entering year three of medicine based on the highest cumulative score of all science courses taken during year one and two of medicine, *2003*.

20. **American Society for Clinical Pathology Award for Academic Excellence and Achievement:** awarded to one student per medical school in Canada for academic excellence in the field of pathology, *2003*.

21. **Marvin L Kwitko Scholarship in Anatomy:** awarded to the student in year one of medicine with the highest standing in anatomy, *2002*.

22. **Rix Family Award in Pathology:** awarded to the student in year one of medicine with the highest standing in pathology, *2002*.

23. **J.B. Campbell Memorial Scholarship in Physiology:** awarded to the student in year one of medicine with the highest standing in physiology, *2002*.

Academic Activities:

Committee Membership:

1. Evidence Based Reviews in Surgery Steering Committee, *2008-2009*.

2. Ontario Association of General Surgeons, program representative, *2009-2011*.

3. **Chair**, Resident Committee, Canadian Association of General Surgeons, *2006-2008*.

4. Post-Graduate Education Committee, Canadian Association of General Surgeons, *2006-2008.*

5. Canadian Surgical Forum Planning Committee, Canadian Association of General Surgeons, *2006-2008.*

6. Residency Training Committee, Division of General Surgery, University of Western Ontario, *2006-2008.*

7. Resident Selection Committee, Division of General Surgery, University of Western Ontario, *2006-2009.*

Administrative Positions:

1. Chief Vascular Surgery Fellow, Victoria Hospital, *July 2011 - June 2012.*

2. Chief General Surgery Resident, Victoria Hospital, *January – April 2011.*

3. Chief General Surgery Resident, University Hospital, *January – June 2010.*

Courses Attended:

1. SAGES Laparoscopic Colorectal Surgery Course, *London, Ontario, February 2010.*

2. Principles and Practice of Clinical Research for Surgeons, *Mississauga, Ontario, November 2008.*

Professional Memberships & Development:

Professional Memberships

1. International Society for Vascular Surgery , member *2012-present*

2. Canadian Association of General Surgeons, resident member, *2005-2011.*

3. American College of Surgeons, resident member, *2006-present.*

Professional Development

1. Fellow Royal College of Surgeons Canada, General Surgery, *June 2011.*

2. SAGES Fundamentals of Laparoscopic Surgery Program, *London, Ontario, July 2009.*

3. Principles of Surgery Exam, the Royal College of Physicians and Surgeons, *April 2007.*

4. Qualifying Examination Part II, Medical Council of Canada, *October 2006.*

5. ATLS Provider Course, *July 2005.*

6. ACLS Provider Course, *April 2005.*

7. Qualifying Examination Part I, Medical Council of Canada, *April 2005.*