Incidence, risk factors and quality of life in IBD : Inflammatory Bowel Disease registry South Limburg

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**Incidence, risk factors and
quality of life in IBD**

Inflammatory Bowel Disease Registry South Limburg

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Incidence, risk factors and quality of life in IBD

Inflammatory Bowel Disease Registry South Limburg

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Chapter Ia

Introduction

Epidemiology of Inflammatory Bowel Disease: an update

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Scand J Gastroenterol 1996; 31: 417-427

Introduction

The terms ulcerative colitis (UC) and Crohn's disease (CD) designate a group of inflammatory diseases of the large and small intestine whose interrelationships remain obscure. The term 'Inflammatory Bowel Disease' (IBD) is often used to delineate these two chronic diseases of unknown origin. UC is primarily a mucosal disease with almost exclusive colonic involvement, whereas CD can appear with mucosal to transmural inflammation in every part of the gastrointestinal tract, but is mainly localized in the ileocolonic area. Current therapy for CD and UC is supportive, immuno-suppressive and non-specific. The first signs of these chronic diseases often develop at an early age; early recognition, good management and continuity of care may have important consequences for the quality of the individual's life.

Descriptive epidemiology

IBD is relatively common in most industrialized countries in the world. Differences in geographical distribution and, particularly changes in incidence over time within one area, may provide insights into possible aetiological factors.

Incidence

The incidence varies greatly with geographic location and ranges from about 1 to 10 per 100,000 and year for CD and from 5 to 18 for UC. The highest rates are reported in Scandinavian countries and Scotland, followed by England and North America while IBD seems to be less common in Central and Southern Europe¹⁻¹⁶. IBD appears to be uncommon in developing countries, but accurate data are lacking for most of those areas^{17,18}.

Comparing incidence rates

Comparing incidence rates between different areas can be misleading because of differences in diagnostic facilities and disease definition. As case ascertainment improves in rural and developing areas, incidence rates may show an artificial increase. As most locations do not have true population-based registries, surrogates (such as hospitalization figures) are sometimes used to estimate incidence^{6,19}.

The variation in the reported series on UC incidence is partly determined by whether or not ulcerative proctitis is seen and recognized by a physician and whether it is included in the UC group^{20,21}. Another important factor that has to be considered is the method of case collection (prospective or retrospective or both).

Table 1a.1 summarizes incidence rates from a number of registries. There seems

to be little doubt that the disease varies with geography. The incidence of IBD seems to have a relation to the degree of industrialization. The distribution also suggests a North-South gradient in Europe and in the United States. The results of a study of Sonnenberg, using data on hospital discharges over a 2-year period and mortality statistics, are in favour of the latter hypothesis²². The recent European Study on IBD detected some differences between the North, Middle and South of Europe but not as large as was expected²³. The mean annual incidence for the two diseases in all areas together was 11.2 for UC and 5.9 for CD.

Table 1a.1 Recent incidence rates (per 100.000 person years) of Inflammatory Bowel Disease of selected areas^{3,4,8,13,32,33,41,49,55,175-190}

Country	Area	Study Period	CD	UC	Collection*
Norway	Western Norway	1983-1986	5.3	14.8	P
Sweden	Orebro	1978-1987	6.8	13.1	R
Denmark	Copenhagen	1979-1987	4.1		P
		1962-1987	8.1		P
Britain	Aberdeen	1985-1987	11.6		P
	Blackpool	1981-1990	6.7		P
	Cardiff	1981-1985	8.3	7.2	R
Netherlands	Leiden	1979-1983	3.9	6.8	R
	South Limburg	1988-1992	5.5	7.6	R
France	Northern France	1988-1990	4.9	3.2	P
Germany	Ruhr area	1980-1984	4.0	2.9	P
Italy	Florence	1978-1987	1.5	4.0	R
Spain	Granada	1979-1988	0.9	2.0	R
Yugoslavia	Zagreb	1980-1989	0.7	1.5	P
Greece	Epirus	1982-1991	0.3	4.0	R
Israel	Southern Israel	1987-1992	4.2	5.8	R
	Beer Shiva	1980-1985			R
USA	Olmsted County	1978-1982	4.3		R
	Baltimore	1977-1979	3.1	2.2	H,R
South Africa	Capetown (whites)	1980-1984	2.6	5.0	R

* Collection of cases: P: prospectively; R: retrospectively ; H: hospital serie

Time trends in incidence

Analysing time trends within an area prevents most of the difficulties described. **Figure 1a.1** illustrates longitudinal data of some centres^{3,7,8,24}. In the Western world, the most rapid increase in the frequency of CD occurred during the period 1965-1980, and, after a slower increase, reached a plateau in most centres and subsequently decreased in some²⁵. Part of this increase could be due to changing diagnostic practices, shortening the time interval between disease onset and diagnosis. A diagnostic transfer from UC to CD is not likely given the fairly steady rates for colitis. The impact of changing diagnostic practices, however, like an increased recognition of CD limited to the colon, cannot be totally ignored. However, most of the increase seems to be real and the rapidity of change suggests that some environmental factor(s) are responsible, since changes in genetic factors are not expressed that quickly²⁵.

Figure 1a.1 Incidence rates (per 100,000 and year) of Crohn's disease of some selected areas^{3,7,8,24}.

The incidence of UC has remained fairly stable in those centres where data have been available for a number of years. However, as shown in **Figure 1a.2**, also in UC there is a tendency towards increasing incidence over the years^{4,26,27}. Epidemiologic data of the county of Copenhagen indicate a six-fold increase in CD, in all age groups and both sexes, in the 25 year interval from 1962 to 1987, with a more stable incidence pattern for UC during the same period^{3,27}. One epidemiological feature of interest is the fact that the incidence of UC is always greater than that of CD when first studied, but that over successive decades the incidence of UC tends to level off, whereas that for CD tends to increase steadily²⁸⁻³⁰. The different time trend for CD and UC suggest that the causal agent(s) or risk factor(s) for UC and CD are different.

Figure 1a.2 Incidence rates (per 100,000 and year) of ulcerative colitis of some selected areas^{4,26,27}.

Prevalence

Determining accurate prevalence rates, referring to the number of cases at one moment, creates certain problems. For example, how to be aware of the number of all patients with UC in remission after colectomy? And should this group be considered in prevalence figures at all? Chronic proctitis can have long periods of disease-free interval, during which time no medical consultation takes place. Follow-up of the initial incident cohort can be rather difficult and asymptomatic patients are probably underestimated in prevalence figures. Incidence figures, especially of prospective studies, are therefore more likely to be correct than prevalence figures.

Age

Both CD and UC mainly become manifest during late adolescence or early adulthood, with a peak onset between 15 and 30 years of age. In most, but not all, series there also appears to be a second, smaller peak at ages between 55 to 80^{1,2,31-36}. Bimodality is more consistently evident for CD than for UC and is mainly observed in some smaller American series. A bimodal age distribution could imply different risks at different ages or also a heterogeneous disease entity. The suggestion that mesenteric vascular disease may account for the secondary rise is attractive, but so far pathologic findings do not support this hypothesis³⁷⁻³⁹.

The incidence of UC in patients under the age of 10 is rare, but far exceeds that of CD. Case ascertainment in the paediatric population may be more difficult since

children with minimal symptoms will probably never be seen by a physician⁴⁰.

Sex

Women are in general at a 20-30% greater risk than men of developing CD. The reports on sex differences in UC are variable, but there seems to be a tendency to a male preponderance^{16,25,41}. It is not clear what implications the sex difference has on the aetiology of either disease, but it suggests that susceptibility for the two diseases may be different.

Mortality

Death rates in IBD patients in the United States and Europe are currently in the range of 2 to 6 per million per year⁴². In particular the elderly and those who have undergone a colectomy in the preceding year seem to be at increased risk of death⁴³. Longterm survival has greatly changed over the decades. While a cumulative 20-year mortality rate of 40% was published in 1963, more recent studies report much better survival, and some even suggest there is no increased mortality in subjects with IBD, compared to the general population⁴⁴⁻⁴⁶. Some of the reported difference in survival between studies can be attributed to differences in disease severity. It seems likely that several other factors, like better medical management and earlier surgery with improved postoperative care, at least partly account for the observed improvement in survival during the last two decades.

Pathogenesis

The pathogenesis of CD and UC probably involves an interaction between genetic and environmental factors (**Figure 1a.3**). While the precise mechanism responsible for initiating intestinal inflammation remains unclear, there is ample evidence for a perpetuation of the disease by an intense and prolonged local mucosal immune response, associated with recruitment and activation of lymphocytes and macrophages⁴⁷. In other words IBD seems to be characterized by a failure to down-regulate a normally self-limited inflammatory response of the gut. The factor(s) triggering this response is (are) presently unknown, but are most probably multiple. Therefore hypotheses based on single aetiological factors might not lead to efficient therapeutic strategies⁴⁸.

Figure 1a.3 Theoretical model of interactions between genetical and environmental factors in IBD.

Intrinsic aetio-pathogenetic factors

Ethnicity

Within geographic areas there are ethnic and racial variations in the incidence of IBD. There is a remarkable predominance of Jewish patients in the North American and South African series⁴⁹⁻⁵². Incidence rates of UC and CD in Israel are higher among those born in Europe or America, compared to those born in Israel^{53,54}. The much lower incidence among Jews elsewhere, and the inconspicuous incidence of IBD in Israel, with even a low incidence in the Israeli-born population, are in agreement with a role of environmental factors in the pathogenesis of IBD. The previously observed difference in CD seems to narrow according to recent studies from Israel reporting that CD has become more common in Jews in Israel -losing ethnic differences of frequency- and that it occurs at an earlier age than before^{55,56}.

In England Hindus and Sikhs appear to have a lower incidence of CD and a higher incidence of UC than the general population; a firm association could not be detected with differences in dietary intake or smoking habits⁵⁷⁻⁵⁹.

From 1960 to 1980 American black and Indian populations were at low risk for IBD. The difference to the American Caucasian population appears to be closing with time, possibly reflecting the disappearance of a differential quality of health care in some areas⁴⁰.

Genetics

There is an increased frequency of positive family histories of IBD among cases of IBD compared to controls (10 to 20%), compatible with a role of genetic factors involved in the susceptibility to CD and UC⁶⁰. UC is increased among the relatives of UC patients, and CD -to a somewhat greater extent- among CD relatives. The two diseases also do occur in the same family with an increased frequency higher than just the co-occurrence by chance alone, suggesting an aetiological relationship between UC and CD⁶¹. The most useful data are empiric risk rates that have been adjusted for the ages of the relatives at risk, thus creating life time adjusted risks as reported by Roth⁶². The age adjusted risk for relatives is highest for siblings and offspring (8-9%), followed by that for parents (3-4%), while the risk for second-degree relatives seems not to be increased⁶³. Family aggregation can have both genetic and environmental causes. The higher concordance rates of IBD, in CD more than in UC, in monozygotic twins than in dizygotic twins, support the argument that genetic factors are an important component in the development of IBD, and that such genetic factors account for much of the familial aggregation⁶³⁻⁶⁵.

Recently Toyoda published the important observation that particular phenotypes of disease may have defined genotypic association⁶⁶. It has been firmly established that perinuclear antineutrophil cytoplasmic antibody (P-ANCA) is a frequent finding in UC but not in CD⁶⁷⁻⁷¹. The increased frequency of P-ANCA in healthy first-degree relatives to probands with UC raised the hypothesis that P-ANCA may be genetically determined^{72,73}. The role of P-ANCA as a subclinical marker of genetic susceptibility to UC was not confirmed in a recent study in monozygotic twins with IBD⁷⁴.

Studies on the role of the HLA system, using serological techniques, have been largely inconclusive for CD, and have shown an increase in the frequency of the HLA-DR2 allele in UC^{66,75}. This increased frequency of HLA-DR2 may provide important clues to aetiology, as this antigen has been associated with increased susceptibility to infection and with increased susceptibility to multiple sclerosis. HLA-B27 and -B8DR3 are only present in cases of IBD in association with ankylosing spondylitis or primary sclerosing cholangitis.

Extrinsic aetio-pathogenetic factors

Infection

Inflammatory bowel disease might be precipitated by infections that either are not searched for at onset, or have been transient, or are still not identifiable by current laboratory methods. The increased incidence of IBD in centres in the Western

world over a relative short period after the Second World War may in part be explained by an infectious agent^{3,4,7,8,76}. The same is true for clustering of cases in time and space and the observed, but also challenged, seasonal variation in the clinical presentation of IBD^{7,77-80}. Finally, the recently described pattern of emergence of IBD in ten married couples in France and Belgium suggest a role for an infectious agent, yet to be identified⁸¹.

A low exposure of infants to enteric organisms (programming the immune system of the gut) as a consequence of improved domestic hygiene could render the bowel more susceptible to a triggering infection later in life. This hypothesis is supported by a case-control study from the UK, showing that CD (but not UC) was more common in subjects with a hot water supply and bathroom in the childhood home⁸². Such findings may explain why the incidence of CD has risen in the developed countries over the past 50 years. The incidence of CD in developing countries may increase as domestic hygiene improves.

Infection with *Mycobacteria paratuberculosis* has strongly been invoked as a cause for CD⁸³⁻⁸⁶. The organism has been isolated from the tissues of only a few patients and attempts to show *Mycobacteria paratuberculosis* DNA in tissues have been variably successful⁸⁷. Seven controlled studies, involving different anti-mycobacterial drugs, have been reported but their results are conflicting⁸⁸⁻⁹². Clinical trials in CD are fraught with difficulties like definition of a homogenous group, the choice of drug(s), duration of therapy and interpretation of results. Lack of response does not exclude the possibility of mycobacteria initiating the disease and improvement in symptoms does not necessarily support the hypothesis⁹¹. The case for or against mycobacteria as a causative agent of CD has not yet been closed.

Viruses that have been isolated in IBD are Cytomegalovirus, small RNA virus, and rotavirus or reovirus-like agents⁹³. Lately morphological and epidemiological studies have implicated measles virus as a potential component cause in CD, particularly when exposure occurs in utero or early in life⁹⁴⁻⁹⁶. Exposure to a measles epidemic as a risk factor in CD could not be confirmed in a large case-control study in the UK⁹⁷. Increased prevalence of CD and UC was found in people who had received live measles vaccine compared to a non-vaccinated group, suggesting that measles virus may play a role in the development of CD and UC⁹⁸.

Dietary habits

A high intake of refined sugar and starch, before as well as after diagnosis, is a remarkably consistent finding in patients with CD, in contrast to patients with UC who do not differ from controls in this respect⁹⁹⁻¹⁰³. There is no self-evident mechanism for the action of sugar to promote the development of CD. In a case-control study by Järnerot sugar intake was only higher in cases after diagnosis of CD¹⁰⁴. This finding suggests that it is a consequence of the symptoms rather than a

cause of the disease.

Another consistent dietary finding in CD concerns the intake of fresh fruit: several case-control studies have found fresh fruit intake to be significantly reduced in CD patients¹⁰⁵⁻¹⁰⁷. In various studies the daily intake of dietary fibre is reported to be either increased or decreased^{187,97,108}. Recently frequent consumption of fast food has been linked with UC and CD in a case-control study¹⁰⁵. However, the number of exposed subjects in that study was small.

Fat consumption (quantitative and qualitative) is of interest in the light of pathophysiological hypothesis related to the inflammatory cascade in IBD, in which the arachidonic acid and cyclooxygenase mediated pathways are involved. An Italian case-control study showed that patients with CD, but not with UC, had a slightly lower intake of fat (total fat and the saturated fatty acid component) before the first disease manifestation compared to controls¹⁰³. Analysing the results of dietary factors, one should realise that the pre-illness diet is of importance. Bearing in mind that in CD the lag between onset of symptoms and diagnosis sometimes can exceed five years, it is not surprising that the attempts to link specific dietary factors with the development of IBD have run into major difficulties.

Early life influences

Breast feeding in early life might reduce the risk of developing UC and CD, as it stimulates growth and development of intestinal mucosa and may provide protection through increased levels of IgA^{97,109-112}. Results of case-control studies are controversial in this respect and, also here, one should realise the great risk of recall bias.

Perinatal infections in genetically predisposed individuals may alter the immune system, and result in clinically overt IBD later in life, after exposure to a yet undefined immunological event. In agreement with this are the findings of a Swedish case-control study showing a four-fold increased risk for IBD in children with a "health event" in the perinatal period⁹⁵. These events included infections in mothers before and after delivery, and especially postnatal infections in the child, which were mainly of respiratory and gastrointestinal origin. Measles infection has been discussed in the previous paragraph.

Occupation and social class

Most, but not all, studies report a higher incidence of IBD in people of higher socio-economic class^{97,106,113,114}. Obviously referral bias is important in this respect and has to be ruled out if possible. IBD is generally acknowledged to be more common in urban populations, although the literature is conflicting on this point¹¹⁴. Transmission of infectious diseases, possibly related to IBD, occurs more often in overcrowded areas, but socio-economic factors may also play a role. It has been

suggested by Sonnenberg, investigating the risk of IBD for different types of occupation, that work in the open air and involving physical activity is protective whereas work in air-conditioned, artificial conditions, with irregular shift work, increases the risk of IBD¹¹³.

Psychosocial factors

The belief that IBD is a psychosomatic disease dates back to the early 1950s. More recent studies have reached different conclusions. In CD the prevalence of anxiety, passive dependency and depression was reported to be higher than in controls by some, but other investigators found little psychopathology¹¹⁵⁻¹¹⁸. One is not surprised by such findings in a chronic disease with so many uncertainties and repercussions on social life. UC patients do not show elevated levels of psychopathology^{119,120}. Major stressful events, however, can initiate a relapse in UC, as was shown by Duffy et al.¹²¹. Stress-exposed subjects were more than twice likely to have a relapse within four to six months.

Thrombogenic factors

a. Smoking and non-smoking

During the past decade, smoking behaviour has been identified as a strong, perhaps the strongest, exogenous risk factor in IBD. In this context UC and CD seem to be opposites. Non-smoking is associated with UC¹²²⁻¹²⁸. Ex-smokers seem to be at even higher risk of developing UC than never-smokers, suggesting either a cessation of smoking due to very early symptoms of the disease or a brief induction time of the protective effect of smoking on UC¹²⁹. A meta-analysis of selected studies demonstrated a dose-response pattern with a decreasing risk of UC with increasing former usage of cigarettes¹³⁰. A case-control study showed that childhood exposure to passive smoking reduced the risk of UC, but not significantly¹³¹. In addition, smoking has been reported as preventing pouchitis in patients with restorative colectomy for UC¹³². It has been suggested that the protective effect of smoking in UC is due to nicotine¹³³. Clinical trials using transdermal or oral nicotine show variable results on disease activity in the acute stage, but no effect of smoking in maintaining remission¹³⁴⁻¹³⁶.

In contrast to UC, smoking appears to be directly associated with the development of CD^{126,130,137,138}. This relationship is more evident for women than for men and not as strong as in UC¹²⁴. No consistent dose-response relationship has been shown, but duration of smoking and childhood exposure to passive smoking both appear to be important determinants¹³⁹.

Smoking behaviour is not only associated with the first outbreak of disease but also influences the clinical course of UC and CD. The presence of a smoking history delays the onset of UC, and in this group extensive inflammation is less frequent

compared to patients with a non-smoking history¹⁴⁰⁻¹⁴². Studies using the number of hospitalizations and colectomy as a marker of disease activity report either a favourable effect of smoking or no relationship in UC^{143,144}. In CD, smokers have more symptoms and, after a surgical resection, the risks of clinical, endoscopic and surgical recurrence are increased in smokers compared with non-smokers¹⁴⁵⁻¹⁴⁷. One of the reasons for the observed change in male:female ratios in UC, which was once a disease with female dominance and now seems to have become a disease with a male dominance, is possibly related to the fact that men tend to give up smoking, while women start smoking¹⁴⁸.

b. Oral contraceptives

Conflicting associations between the use of oral contraceptives and the development of IBD have been reported¹⁴⁹⁻¹⁵⁴. A recent meta-analysis of 16 selected studies found a modestly increased risk of developing CD in oral contraceptive users (RR: 1.44; 95% CI, 1.12-1.86) but failed to demonstrate a significant association between oral contraceptive use and development of UC (RR: 1.29; 95% CI, 0.94-1.77)¹⁵⁵. A large population-based case-control study showed an increased risk for both diseases in women using oral contraceptives within six months before disease onset compared to never users¹⁵⁶. Higher UC risk occurred among users of high oestrogen dose oral contraceptives, while CD risk was similar regardless of oestrogen potency.

c. Hypothetical mechanisms of thrombogenic factors in IBD

The oestrogen component of contraceptives is associated with an increased risk of thromboembolic disease, and risk appears to rise with increasing dose¹⁵⁷. Persistent activation of coagulation in IBD has been shown^{158,159}. In CD vascular abnormalities are more pronounced than in UC. Wakefield et al. have proposed as a pathogenic mechanism for CD multifocal gastrointestinal infarctions mediated by a chronic mesenteric vasculitis¹⁶⁰⁻¹⁶². The pro-coagulant effects of smoking, with subsequent vasoconstriction and infarction of the small bowel arteries, may be of importance in CD. Smoking in this context also may interact with other potentially disease-provoking factors like oral contraceptives¹⁶¹. The results of epidemiological studies on smoking and -to a somewhat lesser extent- of those on contraceptives are in favour of this hypothesis.

The potential mechanisms for the protective effect of smoking and the possible harmful effect of contraceptive use in the pathogenesis of UC are less clear. Smoking has a number of known effects on immune and inflammatory functions. Heavy smoking results in alterations in immunoregulatory T cells, and there is also evidence that smoking increases colonic mucus production *in vitro*^{163,164}. Smoking inhibits the release of leukotriene B₄, thus reducing cell chemotaxis, and decreases the production of interleukin-1 from these cells, and in addition influences the

function of circulating neutrophils¹⁶⁵⁻¹⁶⁷. Another possible mechanism is that smoking may protect by lowering the rectal blood flow in patients with UC¹⁶⁸. Finally, an interesting theory poses that altered bile composition, by enhancing (smoking) or inhibiting (contraceptives) hepatic P-450 enzyme, may decrease or increase UC incidence¹⁶⁹.

Miscellaneous aetio-pathogenetic factors

Allergy

A significant higher incidence of (atopic) eczema has been reported in patients with IBD or their families than in appropriate controls¹⁰⁶. Atopic eczema is usually associated with a higher incidence of allergic rhinitis and asthma. There are many similarities between asthma and inflammatory bowel disease. Both inflammatory processes are characterised by spontaneous exacerbations and remissions, and similar inflammatory mediators contribute to their pathogenesis¹⁷⁰. On the other hand the T-helper cell population, of importance in the pathogenesis, in both diseases is clearly different. While in CD low levels of the anti-inflammatory Interleukins 4 and 5 are found, those Interleukins are high in asthma.

Toothpaste

Ingested materials, like talc and ingredients of toothpaste, can produce granulomatous lesions in the bowel resembling those in CD. So far the subject of toothpaste as a risk factor for CD gave rise to interesting epidemiological discussions, but has not been shown to be of real importance^{112,171-173}.

Appendectomy

Three case-control studies showed a strong negative relation between appendectomy and the development of UC^{82,106,174}. The explanation for this inverse association is unclear. Factors predisposing for appendicitis may protect against UC, or removal of the appendix may alter the immune response of the gut. One of these studies also showed a tendency to a positive relation between appendectomy and CD⁸².

Summary and conclusions

What have epidemiological studies on IBD taught so far? Consistent findings are:

- A high incidence for both CD and UC in industrialized countries and an increase in these areas of the incidence of CD during the years 1960-1980 followed by a plateau phase, and a more stable pattern in UC during the same period. A greater number of mild cases have probably been diagnosed recently. This also helps to explain the differences in severity and survival between community and referral centre groups.
- The male to female ratio is greater than one in UC, and this is the opposite in CD.
- Mortality of IBD has decreased during the last decades. As young people are especially prone to develop IBD, most of those affected will have their disease for many years.
- In developing IBD genetical influences are of importance. However, epidemiological studies strongly point to possible interactions between genetically determined features and environmental or other factors. Of these exogenic factors smoking is the most consistent, being of negative influence in CD and protective in UC. Diet and oral contraceptives may influence disease expression, and perinatal events -like viral infections- may alter adult susceptibility.

The question remains open whether UC and CD are one disease entity. Similarities in the epidemiologic features of UC and CD support the idea of IBD as being one disease. Other findings suggest to divide UC and CD further into subgroups: in CD it has been suggested to that fibrostenotic, penetrating and inflammatory behaviour should be considered different disease entities; in UC, some groups consider ulcerative proctitis as a disease entity on its own, separating it from the proximally extending colitis. In therapeutical trials this approach has proved to be of importance and it is not inconceivable that in subgroups, as far as aetio-pathogenetic mechanisms are concerned, different factors have to be looked for.

Preconditions for epidemiological studies in IBD

- Comparing disease rates between different areas and -within areas- at different time intervals can be helpful for our understanding of IBD.
- Cohort studies are gaining popularity and might also lead to valuable new insights. This is only possible if generally accepted disease definitions and comparable methods of case ascertainment are used.

- In order to compare different studies, the incidence rates should be standardised for age and sex. Most valuable are prospective, community-based studies. The European Study on Inflammatory Bowel Disease can serve as an example.
- Population-controls should be used when studying risk factors. Single item studies are of doubtful value, and risk factors should be studied in connection with each other.
- Studying the role of possible risk factors and the effect of therapies in subgroups seems to be of interest. New genetic markers may help to differentiate between these subgroups.

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Chapter Ib

Introduction

Measuring quality of life in Inflammatory Bowel Disease

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The impact of IBD

Crohn's disease (CD) and ulcerative colitis (UC) are two chronic gastrointestinal diseases of unknown origin. The effectiveness of medical and surgical therapy remains limited. Few patients die as a result of their Inflammatory Bowel Disease (IBD). However, many patients pay frequent visits to their general practitioner and specialist. Some require recurrent hospitalizations for problems due to their intestinal disease. This might cause work absenteeism, as well as stress due to uncertainties about future health.

Until recently, measuring the impact of IBD was almost exclusively performed by measurement of clinical disease activity, using activity indices or endoscopic appearance in clinical trials¹⁻⁴. Recent investigations show that measures of disease activity for IBD are insensitive and discrepant with patient perceptions of their health status⁵⁻⁷. Quality of life measures such as functional status and disease-related concerns correlate better with scores of well-being and health care utilisation than the physician's rating of disease activity⁸.

Health-related quality of life (HRQoL), also called health status, is a global concept that incorporates the patients' perceptions, attributions, and daily level of function in response to an illness. HRQoL is influenced by social, cultural, psychological, and disease-related factors and differs from measurement of symptoms and signs in that evaluation includes psychosocial as well as disease-related factors⁵. Typical areas of HRQoL which are evaluated include well-being, pain and discomfort, body image, sexuality, ability to perform activities of daily living, participation in social or recreational activities, ability to work, to attend school and to engage in personal relationships⁹. Standardised instruments have been developed during the last decade to measure various aspects of HRQoL. Three main types of instruments include global assessments, generic instruments and disease-specific instruments (Table 1b.1).

Global measures

The simplest approach is to use a single question, for example: "How would you rate your general well-being?" The response can be rated on a scale such as "excellent-good-fair-below average-poor". The response provides a clinically relevant global measure that is a strong predictor of physician visits for patients with IBD⁷. The major disadvantage of a global measure is that it cannot identify the reasons for good or poor HRQoL.

Table 1b.1 Types of HRQoL measures used in Inflammatory Bowel Disease

HRQoL	Description	Comments
Global assessments	Unidimensional <i>Example</i> - “good”, “fair”, “poor”	Unable to identify factors leading to positive /negative outcome
Generic measures	Multidimensional <i>Examples</i> - Sickness Impact Profile - Nottingham Health Profile	Insensitive to subtle changes with time
Disease-specific instruments	Multidimensional Disease specific <i>Examples</i> - IBDQ - Cleveland Clinic Questionnaire - Rating Form of IBD Patients Concerns - UC/CD Health Status Scales	Most sensitive to detect important clinical changes

Generic measures

Generic measures evaluate HRQoL independent of the specific features of the disease and permit comparisons among diseases, populations, or interventions. In contrast to global measures these are multidimensional instruments, incorporating several domains of experience and behaviour, such as perceptions of disease, or physical or psychological functioning¹⁰. There are two basic types of generic measures: *utility measures and health profiles*¹¹⁻¹³.

Utility measures relate self-perception to a reference point. For example the “Time Trade-Off Technique” evaluates the patient’s perception of existing health compared with death¹⁴. The score ranges from 0.0 (equal to death) to 1.0 (full health) and patients choose between living in the present health with all its problems and living a shorter life span but in perfect health. A utility measure is, similar to global measures, more useful as an evaluative rather than a discriminative measure because the factors leading to the score are not known¹¹.

The Sickness Impact Profile (SIP) is an example of a commonly used *health profile*, which has been used to study QoL in CD. Drossman showed that patients

with IBD had on the overall scale a poorer HRQoL than a random sample of patients with obesity, but a better HRQoL than patients with rheumatoid arthritis, chronic obstructive pulmonary disease, or chronic back pain⁶. Psychological dysfunction appeared to be worse in patients with CD than in those with ulcerative colitis (UC).

Generic measures of HRQoL focus on activities of daily living such as eating and bathing, and fail to emphasise health problems more relevant to the young population with IBD, such as the consequences of blood loss, loose stool or abdominal pain¹⁵. They may therefore be too insensitive to measure true changes in clinical trials employing a therapeutic intervention.

Disease specific measures in IBD

Disease specific questionnaires are multidimensional instruments composed of patient-generated problems, and are the most sensitive instruments for detecting change over time or after intervention⁹. They evaluate special states and concerns of patients having a particular disease. Four disease-specific questionnaires have recently developed to be used in IBD: "The Cleveland Clinic Questionnaire", "The Rating Form of IBD Patient Concerns", "The UC/CD Health Status Scale", and the "Inflammatory Bowel Disease Questionnaire (IBDQ)". The Cleveland Clinic Questionnaire evaluates activities of daily living rather than medical symptoms and the items successfully discriminated patients with milder and more severe disease¹⁶. The Rating Form of IBD Patient Concerns can help clinicians to easily obtain information about the most important worries and concerns of patients with IBD¹⁷. The UC/CD Health Status Scale was developed to discriminate mild from severe illness and has shown to be a stronger predictor of outcome than the CD Activity Index^{4,18}.

The Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific QoL questionnaire, was developed by Guyatt et al. at McMaster University in Canada to measure treatment effects in clinical trials. This well-validated questionnaire has also been used in the South Limburg IBD Registry. During the formulation of the IBDQ, patients as well as health care providers identified 150 problems experienced by patients with CD or UC, which were ranked by the patients according to severity and frequency. The most notable problems were intestinal symptoms, systemic symptoms and emotional dysfunction, whereas social dysfunction appeared less disabling than the other categories. The final questionnaire contained 32 items within four dimensions (bowel, systemic, social and emotional). Responses were graded on a seven-point Likert scale from 7 (not a problem) through 1 (a very severe problem). The questionnaire is psychometrically sound and has been shown to be reproducible, stable, and responsive to change in

an IBD population¹⁹.

Validation of measurements

All types of instruments need to be valid (measure what they are supposed to measure), reliable (give comparable result if measured repeatedly), discriminative (able to detect differences between groups of patients with different stages of diseases), and sensitive to change (able to measure change over time)^{11,20}. Since psychosocial determinants are not accessible through laboratory tests, validation rests with the patient⁵. Only two European countries have English (the language being used in most HRQoL instruments in IBD) as their native language. For other countries to be able to set up or participate in international clinical trials, it is necessary to either use a validated translation of the instrument or to develop a new instrument. To use a questionnaire like the IBDQ in respondents with a native language other than English requires translation, back-translation, and re-establishing the validity and reliability within the new national context²⁰.

Conclusions

Clinicians and investigators in the field of IBD have come to realise that disease-related biological measures such as laboratory findings, histopathology, endoscopic/radiological findings do not adequately reflect the health status of patients with CD and UC¹⁰. The evaluation of HRQoL can broaden our understanding of the impact of these disorders in a manner that cannot be accomplished through traditional methods. HRQoL is important for measuring the impact of chronic diseases. At present there are few well validated disease specific QoL instruments. Most HRQoL instruments are developed to be used in clinical trials, but it might be worthwhile to investigate their use in daily patient care and to study the influence of environmental factors on disease outcome. Their use beyond clinical trials and in countries with native languages other than English remains to be elucidated.

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Chapter Ic

Introduction

Thesis outline and aims of the study

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Thesis outline and aims of the study

The present thesis reports the development of a population-based Inflammatory Bowel Disease Registry in South Limburg, The Netherlands (**Chapter II**). This Registry has enabled us to prospectively study the incidence of Inflammatory Bowel Disease (IBD) and to investigate genetic and environmental risk factors. The following aims are addressed in this thesis:

Frequency of IBD in the study area

- To prospectively investigate the incidence and the clinical features at presentation of patients with Inflammatory Bowel Disease living in South Limburg, The Netherlands (**Chapter III**)
- To assess the quality of the calculated incidence data, using the Registration Network of General Practitioners (RNH) as a reference (**Chapter III**).

Genetic and environmental risk factors of IBD

- To study familial aggregation of Inflammatory Bowel Disease in a well-defined selected group of the prevalent and incident patients registered at the IBD Registry South Limburg (**Chapter IV**).
- To study a possible association between 'modern life nutritional factors' and the risk to develop IBD in recently diagnosed patients using multiple logistic regression analysis to minimise confounding by other risk factors (**Chapter V**).
- To further elucidate the role of appendectomy as a possible factor influencing the development of ulcerative colitis and in Crohn's disease, in a pairwise matched case-control study (**Chapter VI**).
- To define the role of smoking and disease characteristics at presentation and disease development during the first year of follow-up in a large cohort of incident European IBD patients (**Chapter VII**). To address this question, data of the European Collaborative Study on the incidence of IBD, a concerted action of twenty European Centres, have been used. Part of the patient data originate from IBD patients registered at the South Limburg IBD Registry who were diagnosed between October 1991 and October 1993.

The IBD patient questionnaire, a part of the South Limburg IBD Registry, was also developed to investigate Health Related Quality of Life (HRQoL) in IBD patients. The subject is introduced in **Chapter Ib**. In this thesis the results of two studies on quality of life are described, which had the following aims:

- To validate the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ), to be able to use this instrument in clinical trials in the Dutch-speaking IBD population (**Chapter VIII**).
- To investigate the usefulness of the validated Dutch IBDQ in studying the influence of risk factors on the course of disease. More specifically: to determine to what extent smoking influences HRQoL in IBD patients (**Chapter IX**).

The data that have been generated by the various studies are discussed in more detail and in the light of information from current literature in **Chapter X**.

 

Chapter II

Data management of the South Limburg Inflammatory Bowel Disease Registry

'IBD South Limburg'

MGVM Russel

Introduction

Inflammatory Bowel Disease (IBD) is a summarising denominator for ulcerative colitis (UC) and Crohn's disease (CD). The cause of IBD is unknown. Most data on the clinical course and outcome of UC and CD originate from referral centres with a special interest in IBD. After a period of progression during the sixties and seventies, the incidence of CD in the Western world seems to have reached a plateau, and in the same time period the incidence rate for UC has stabilised in northern Europe and North America.

UC is primarily a mucosal disease involving the colon and rectum. It is characterised by abdominal cramps, rectal bleeding, diarrhoea, urgency, and systemic signs of inflammation. CD, a transmural inflammation, can occur in every part of the gastrointestinal tract, but is mainly localised in the ileocolonic area. Signs of CD include narrowing and obstruction of the bowel, abscess and fistula formation, and sometimes perforation. Systemic problems involving the eyes, joints, skin, and hepatobiliary system are also associated with IBD.

There is no established cure for either disease and current therapy is supportive, immunosuppressive, and non-specific. Research on the cause(s) of IBD focuses on genetics, environment (including diet), circulatory factors and immunology.

Given this background of IBD, a population-based Inflammatory Bowel Disease Registry was established in 1991 in collaboration between the Departments of Gastroenterology / Hepatology and the MEMIC (Centre for Data and Information Management, University of Maastricht). The primary objective was to prospectively study the incidence of IBD and to investigate risk factors within a stable population in a large well-defined geographical and administrative area identified as South Limburg. Beyond this, the protocol of the study was also designed to study clinical features and quality of life in IBD. Secondary aims of the Registry were stimulation of the co-operation between clinicians in the field of gastroenterology and foundation of a study base for other clinically-orientated studies in IBD.

Background area and population

South Limburg is located in the south-east of The Netherlands and is a well-defined geographic entity, which bounds on Germany to the east and on Belgium to the south and west, while the northern border of the area is very narrow.

The region had an average population of 642.240 during the 1991-1994 period. The health care system in The Netherlands is regionally organised. In South Limburg there are six hospitals. Besides the University Hospital in Maastricht, the general district hospitals of Heerlen and Sittard, and three smaller associated

hospitals (Geleen, Kerkrade and Brunssum) also participated in the study. IBD patients are normally referred to these hospitals for out- and in-patient care by about 300 general practitioners working in the area. To our knowledge, no patients with IBD living in the study area are treated in private practices, and only a small minority in hospitals outside the study area or abroad.

Participation of clinicians, general practitioners, and patients

During the preparatory period, clinicians treating IBD patients in the study area were visited by the main investigators and were asked on their opinion about the project and whether they were willing to actively participate in the study. Since most of the clinicians were enthusiastic about the basic idea, the next step was to visit the general practitioners. During the various discussions with representatives of the general practitioners, it became evident that it would almost be impossible to actively involve all general practitioners in the area. Hence it was decided to cooperate with the Registration Network of General Practices (RNH) in South Limburg instead. This registry contains files with most diagnoses, including IBD and its subgroups, of 47.850 patients (7.5%) of the total population living in the study area known to 35 general practitioners who have direct electronic connection with the RNH. Finally, as an important step, meetings with representatives of the Crohn's and colitis patient association were organised to discuss the usefulness of a regional IBD Registry.

Development of the IBD Registry

The second objective was to define a model of a successful IBD registry that included

- a) a patient *registry form* (**Appendix 1**), which should be easy and quick to complete by specialists
- b) a *patient questionnaire* (**Appendix 2**) that included detailed demographic characteristics, a family history of IBD, information on potential environmental risk factors, and instruments to measure quality of life and quality of care
- c) a *medical data form* (**Appendix 3**) to record relevant medical data of the first six months after the first visit to the specialist
- d) *follow-up medical data forms* to be used at the period after the first six months of IBD
- e) *follow-up patient questionnaires*
- f) a tentative data-entry system

- g) a database (the 'Rolodex') as the only source of personal data such as name, address, and general practitioner of the participants etc., which should be capable of connecting the forms mentioned under a to e and of relating all forms with the purpose of knowing when to send out the different forms to patients and investigators of the study.

The MEMIC had a major role in developing the research structure and the patient data forms. All forms were validated in a selected group of IBD patients in collaboration with the Crohn's and Ulcerative Colitis Association in South Limburg. The IBD Registry was subsequently announced at the Dutch Person Registration Office and approval was given to collect patient data. All patients had to give informed consent before registration could take place. In the event that no informed consent was obtained, only non-traceable information was recorded to be able to study the incidence of IBD. Subsequently data entry of the *patient registry form* in the Rolodex was performed at the University Hospital of Maastricht after encoding of the patient data forms by the research assistant. Data entry of the encoded forms was then done at the MEMIC. To minimize mistakes, all forms were entered twice in the system by different data-entry employees. The registration of the first patient started on 1 October 1991.

Registry Form

All physicians and surgeons practising in the area and known to treat IBD patients were supplied with *Registry forms*. They were asked to report all new diagnosed (incident) patients with IBD and as many patients as possible with known IBD before the start of the Registration (prevalent group). Guidelines for the definition of the subgroups of IBD according to the criteria of Lennard-Jones and Truelove and Witts were enclosed in all *registry forms*. In addition to demographic data, the specialist was asked to complete four questions on the diagnosis and first complaints of the patient. The *registry form* is the only data file that contains fields which could specifically identify any patient. An unique IBD acquisition number is assigned to each record and used to link the data files. The patient has to sign that he or she had given informed consent to participate in the study on this form and the medical chart of the patient is marked with a sticker to indicate participation in the study.

Patient Questionnaire

Within six months after registration all patients received the *patient questionnaire*. In case of non-response, the research assistant approached the patients by mail and as a second step by means of a phone call.

Medical Data Forms

Senior medical students were trained by the investigator to complete the *medical data forms* and *follow-up medical data forms* of the IBD patients at the hospital of registration. After return, all forms were controlled by the main investigator and in case of doubt the treating physician was contacted to obtain reliable data. The diagnosis according to the opinion of the main investigator, also using the standardised criteria of disease definition, was added to the form.

Database management

Personal data of the patients are stored in a database ('Rolodex'), which links all the forms by the assignment of an IBD acquisition number to each patient. The 'Rolodex' automatically checks whether the patient has already been registered and whether the patient actually lives within the study area. After encoding of all the forms by the research assistant, data entry is performed at the MEMIC. Updates of the related forms are supplied to the investigators at intervals of circa 6 months. For privacy reasons, the access to the 'Rolodex' is restricted to the main investigator and the research assistant (**Figure 2.1**). This file is physically separated from the others to maximize the data confidentiality.

Figure 2.1 Data management of the South Limburg IBD registry

Control Population

The third objective was to establish a population-based control group to be used in case-control studies when investigating risk factors. They were recruited in cooperation with the Registration Network Family Practices (RNH). Out of 47.750 registered patients at the RNH, all living in the study area and without history of

IBD, a sample of 924 persons was selected, according to sex and age distribution of the IBD patients at January 1994 and with the restriction of having no IBD diagnosis. This group received a *control questionnaire* which lay-out and structure is similar to the *patient questionnaire* in May 1994. This group was also contacted by mail in the event of non-response.

Basic results of the registration

Until July 1996, a total number of 1567 patients were reported to the study centre as having either UC (n=750), CD (n=713) or indeterminate colitis (n=104) according to the study criteria. Five patients reported with only basic data, because of refusal of the patient to participate in the study. Of this group of 1567 patients 592 (38%) were newly-diagnosed, whereas the remaining were already known with IBD at the start of the registration. **Figure 2.2** shows the distribution according to gender for the separate diagnostic subgroups of IBD. In contrast to UC and indeterminate colitis, in CD there was a preponderance for females. The number of patients registered during the first five years, divided into prospective and retrospective patients, is shown in **Figure 2.3**. The number of prospectively diagnosed patients is constant over the years. It has to be remembered that the rates were calculated at July 1996 resulting in low figures for this calendar year. In contrast the number of patients known with a diagnosis of IBD before October 1991 decreases over the years. The cumulative percentage of newly-diagnosed patients as were reported per participating hospital is illustrated in **Figure 2.4**.

Figure 2.2 Number of registered IBD patients at July 1996 according to gender for the separate diagnostic subgroups of IBD at the moment of registration (UC: Ulcerative Colitis, CD: Crohn's Disease, IC: Indeterminate Colitis)

Figure 2.3 Number of IBD patients registered during the first five years, divided into prospective and retrospective registered patients

Figure 2.4 Cumulative percentage of IBD newly-diagnosed patients reported per participating hospital

The response to the *patient questionnaire* in July 1996 was 93% (1452 out of 1567). At that time the data of the medical forms of 1218 patients (78%) had been entered in the database at the MEMIC. In the control group the questionnaire was completed by 616 persons (67%).

Scientific output

The majority of the first analyses of the data of the South Limburg IBD Registry are reflected in this thesis, and have been published or submitted for publication in journals of Internal Medicine or Gastroenterology. The data also served for the European study on the incidence of IBD in the north and south of Europe, a multicentre prospective study during the period 1991 to 1993, including a large scale European follow-up study of this cohort which presently is underway. Furthermore the data are used in several spin-off studies that have originated from the main study such as "Osteoporosis and IBD", "Nutrition in IBD", "Coagulation and Fibrinolysis in IBD", and "Hepatobiliary Complications in IBD". The databases proved to be useful in patient recruitment for clinical trials, and finally it has been used to develop a multicentre protocol on quality of care in IBD.

Conclusion

The South Limburg IBD study was primarily set up to study the incidence of CD and UC and to study risk factors of IBD in a population-based design. This has prompted the development of a population-based Inflammatory Bowel Disease registry. Using an unique IBD identification number enabled us to link different databases whilst maintaining patient privacy. We have found that the design of the IBD registry and its related databases enabled us to manage the data accurately. So far the database has resulted in accurate incidence rates of both diseases in the study area, which can serve as guidelines for studies and planning of medical care. Risk factors could be addressed in a population-based study design. The secondary goal, validating and testing quality of life in IBD, has also been successful. In the near future the registry has to prove its usefulness in the follow-up and long-term investigation of the incidence of IBD and in the spin-off trials.

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Chapter III

High incidence of Inflammatory Bowel Disease in The Netherlands: results of a prospective study

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Abstract

Purpose: In order to gain recent epidemiological information about Inflammatory Bowel Disease (IBD) in The Netherlands, a prospective study over 4 years (1991-1995) was carried out.

Methods: The incidence of IBD and its subgroups was examined using standardised reports of newly-diagnosed patients. A separate study compared the IBD Registration and computerised diagnostic files of a subgroup of general practitioners with the aim of estimating completeness of case ascertainment.

Results: The following mean incidence rates (per 100.000 inhabitants and year) were found: 6.9 (95% CI: 5.9-7.9) for Crohn's disease, 10.0 (95% CI: 8.7-11.2) for ulcerative colitis - 23% of these with ulcerative proctitis - and 1.1 (95% CI: 0.7-1.5) for indeterminate colitis. In the age category 20-29 years the incidence rate of Crohn's disease with small bowel involvement was higher in females than in males. In extended ulcerative colitis a male preponderance was observed in the older age groups. Estimated case ascertainment was 100% in Crohn's disease, 80% in extended ulcerative colitis, but only 25% in ulcerative proctitis.

Conclusions: Compared to recent studies in neighbouring countries, the observed age and sex standardised incidence rates are high in the South of The Netherlands. Completeness of case ascertainment might have contributed to this observation; however, case ascertainment was low in ulcerative proctitis. In the study area, differences in age and sex standardised incidence rates, and in disease localisations, could be compatible with an influence of exogenic risk factors.

Introduction

While the number of newly-diagnosed cases of Crohn's disease in Western Europe has increased since the 1950s, the incidence of ulcerative colitis has shown a more stable pattern^{1,2}. In the United States and in Europe, Inflammatory Bowel Disease (IBD) appears to be more common in northern than in southern areas^{3,4}. Differences in genetic background and variable exposure to exogenic risk factors have been mentioned as possible explanations for the inconsistent rates⁵. However, it should be kept in mind that comparison of incidence rates between areas is hazardous, since different methods of case ascertainment and variable diagnostic definitions have been used.

In The Netherlands, so far only one study has addressed the incidence of IBD. In 1987, a retrospective study from Leiden reported incidence rates regarding the period 1978-1981^{6,7}. In order to gain more recent epidemiological information about inflammatory bowel disease in The Netherlands, we conducted a prospective study over 4 years between 1991 and 1994 in South Limburg.

Methods

Background area and population

South Limburg is located in the South East of The Netherlands and is a well-defined geographic entity, which bounds on Germany to the east and on Belgium to the south and west, while the northern border of the area is very narrow (Figure 3.1).

Figure 3.1 Study area South Limburg, a well-defined area situated in the south-east of The Netherlands

The region had an average population of 642.240 during the 1991-1994 period. The exact number of persons, grouped by age and sex, for each of the years 1991-1994 was obtained from the Central Bureau of Statistics of The Netherlands (CBS; age structure Corop 39 (1991-1994); adapted by the Centre for Data and Information Management (MEMIC)).

The health care system in The Netherlands is regionally organised. In the South Limburg area there are six hospitals. Besides the University Hospital in Maastricht, the general district hospitals of Heerlen and Sittard, and three minor associated hospitals (Geleen, Kerkrade and Brunssum) participated in the study. IBD patients with degrees of disease severity ranging from very mild to severe are referred to these hospitals by about 300 general practitioners working in the area. To our knowledge, no patients with IBD living in the study area are treated in private practices, in hospitals outside the study area, or abroad.

Disease definitions and disease location

Cases of IBD were grouped into those with Crohn's disease (CD), ulcerative colitis (UC) or indeterminate colitis (IC). IBD was diagnosed, after exclusion of infections and other recognised causes of inflammation, on the basis of endoscopic and/or radiological evidence, supported -whenever possible- by mucosal biopsy and/or examination of a surgical specimen. The criteria of Lennard-Jones were applied in case definition for CD, taking into account both macroscopic and microscopic features⁸. UC was defined as continuous mucosal inflammation without granulomata, affecting the rectum and/or some or all of the colon in continuity with the rectum. The term "indeterminate colitis" was used for cases of IBD when, after careful investigation, the differential diagnosis between CD and UC remained uncertain.

Using all available medical information obtained during the first six months after diagnosis, localisation of the disease in the large and small bowel was carefully recorded. CD was subdivided into exclusive small bowel disease, exclusive colonic disease, and combined small and large bowel disease. UC was subdivided into ulcerative proctitis (UP) and extended ulcerative colitis (e-UC), depending on whether or not the disease extended proximal to the rectosigmoidal junction. In e-UC a further difference between left-sided colitis (inflammation up to, but not beyond, the splenic flexure) and pancolitis (inflammation beyond the splenic flexure) was made.

Case collection

Gastroenterologists, physicians, surgeons and paediatricians working in the six hospitals were asked to participate in the study. Starting on 1 October 1991, these specialists reported information on their incident as well as prevalent IBD patients

to the study centre on a short "first-report" form. Besides demographic data this form contained questions about the diagnosis according to the study criteria, the date of diagnosis and the duration of complaints. Patients were asked by their specialists to give written informed consent that further information might be obtained and recorded in a database. After six months comprehensive data from the medical record(s) of these patients were collected by specially trained senior medical students. The available medical information on the disease course during the first six months of all incident patients was subsequently examined by one of the authors (MR). In case of disagreement on the diagnostic classification of a case, the medical information was reviewed by a panel of two senior co-workers of the study (R-JB and RWS).

Methods to improve completeness of case ascertainment included searches of the computerised systems of the national pathology database PALGA ("Pathologisch Anatomisch Landelijk Geautomatiseerd Archief"), files of endoscopy units and hospital discharge databases ("Landelijke Medische Registratie") of the participating hospitals. Meetings with participating specialists known to treat IBD patients were held on a regular basis. In the present study, only data of newly-diagnosed (incident) cases living in the study area at the time of diagnosis are used for analysis.

Some of the data on 220 patients in the two-year period starting October 1991 have been included in the European Collaborative Study on Epidemiology of IBD^{9,10}.

Ascertainment of completeness of case collection

To estimate the percentage of missing patients, a separate study was performed with the Registration Network of General Practitioners (RNH) in South Limburg as a reference¹⁰. This Register contains files with all diagnoses, including IBD and its subgroups, of 47,850 patients (7.5%) of the total population of the study area known to 35 general practitioners practising in 13 group practices in the study area. Medical information was collected at the general practitioners' office of all patients with a diagnosis of IBD according to the information of the RNH, who, while living in the study area and registered at the RNH in the study period, were unknown at the IBD Study Centre. Because of privacy reasons these patients were known to us only by initials, gender and date of birth. The same panel, as mentioned above, used this information for diagnostic classification into either non-IBD or CD, UC and IC.

Analysis

Age is reported as median (range). Data on disease manifestation are reported as percentages of patients with positive findings at either first presentation or during the first six months of presentation. The annual incidence rates were calculated

Incidence of IBD

Table 3.2 Annual incidence rates (newly-diagnosed cases per 100.000 inhabitants and year) of Crohn's disease, ulcerative colitis, extended ulcerative colitis, ulcerative proctitis and indeterminate colitis during the study period

	1991	1992	1993	1994	Mean 91-94	(95% CI)
Crohn's disease	6.2	8.9	6.8	5.6	6.9	(5.9-7.9)
Ulcerative colitis	10.0	12.8	9.2	7.9	10.0	(8.7-11.2)
- extended UC	7.2	9.2	7.2	6.3	7.5	(6.4-8.5)
- ulcerative proctitis	2.8	3.6	2.0	1.6	2.5	(1.9-3.1)
Indeterminate colitis	1.2	1.1	0.8	1.1	1.1	(0.7-1.5)

incidence

Figure 3.2 Mean annual incidence rates (per 100.000 and year) of Crohn's disease in different age groups by gender. Every marker represents the mean value of a five years interval

In UC, males in the higher age strata (between 30 and 60 years), had a higher incidence rate than females, mostly caused by the groups of patients with left-sided colitis and pancolitis (**Figure 3.3**). Again the difference between sexes was not statistically significant when the three disease localisations were analyzed separately.

Figure 3.3 Mean annual incidence rates (per 100,000 and year) of ulcerative colitis in different age groups by gender. Every marker represents the mean value of a five years interval

Completeness of case ascertainment

During the first three years (1991-1993) of our registration, 39 new cases of IBD were diagnosed in the 13 general group practices (35 general practitioners) participating in the Registration Network of General Practitioners (RNH). Of those patients 18 were unknown at the IBD Registration. Verification of the exact date of diagnosis and of the diagnostic criteria as used in our study excluded 12 patients, resulting in 6 patients truly unknown to us: 5 with UC (3 of these with UP) and one with IC. Four of these patients were known to specialists in the study area but had not yet been reported. Patients with CD were all known at the IBD Registration. In case that the general practitioners' registration would be defined as reference, the sensitivity of the IBD Registration for IBD would have been 78% (21/21+6) (Table 3.3).

Table 3.3 Sensitivity of the South Limburg IBD Registration defining the Registration Network General Practitioners (RNH) as a reference

	CD nr RNH +	e-UC nr RNH +	UP nr RNH +	IC nr RNH +	all IBD nr RNH +
IBD Reg +	11	8	1	1	21
IBD Reg -	0	2	3	1	6
Sensitivity (%)	100	80	25	50	78

(CD: Crohn's disease, e-UC: extended ulcerative colitis, UP: ulcerative proctitis, IC: indeterminate colitis, nr = number of patients, + : known and - : unknown in database)

Discussion

The incidence rate of inflammatory bowel disease in the South Limburg area, as reported in this study, is high compared to the only available data reported for The Netherlands: in a retrospective study during the period 1978-1981 in the Leiden area, Shivananda and co-workers found incidence rates of 3.9 for CD and 6.6 for UC^{6,7}. As disease definitions in both studies are comparable, the higher rates of our study could either be explained by a more complete case ascertainment due to the prospective approach, or else by a real rise in incidence during the last 15 years. Finally, the difference could be due to a real higher incidence of IBD in our area. Both study populations might then differ because of the genetic background or because certain exogenic risk factors.

The age and sex specific incidence rates of IBD in South Limburg are also higher than in most of the 19 European centres participating in the European Collaborative Study on IBD during the study period October 1991-October 1993¹⁰. Recently published incidence rates of IBD in Western European countries are given in **Table 3.4**^{6,7,12-22}. Compared to these studies the incidence rate of CD in South Limburg is higher than of most other centres. Generally, the Scandinavian countries report a higher incidence of UC than was found in our study. Most striking is the high incidence of UC (10.0 per 100.00 and year) in our study compared to recently published figures of Northern France and the Ruhr area in Germany, geographically close to Maastricht, both reporting low rates (4.9 and 2.9 per 100.000 and year)^{12,14}. Since all these recent studies have used the same or similar disease definitions and study design, the high incidence of IBD in South Limburg seems to be real.

Table 3.4 Recently published incidence rates (per 100.000 inhabitants and year) of IBD in some Western European countries

Country, area, reference	Study period	Incidence per 100.000/year	
		CD	UC
France, Northern ¹¹	1988-1990	3.2	4.9
Italy, Northern ¹²	1990-1993	3.4	7.0
Germany, Ruhr area ^{13,14}	1980-1984	4.0	2.9
Denmark, Copenhagen ^{15,16}	1980-1987	4.1	9.2
The Netherlands, Leiden ^{6,7}	1978-1981	4.9	6.8
Norway ^{17,18}	1990-1993	5.8	13.6
Sweden, Uppsala (Urban) ¹⁹	1965-1983	6.6	11.5
UK, Cardiff ^{20,21}	1981-1985	8.3	7.2
Present study (NL)	1990-1994	6.9	10.0

Fluctuations in the incidence rates during the four years of the registration were small and not significant. Incidence rates of the last study year (1994) are somewhat lower than those of the preceding years. The most probable explanations are a diagnostic delay (which also has been observed in other longitudinal studies) and a time lag between diagnosis and reporting the patient to the IBD Registration¹⁷.

Using the medical information on disease course and investigations during the first six months, half of the patients initially reported as IC could be either classified as CD or UC. The percentage of patients who remained classified as indeterminant colitis (6%) was slightly lower than usually reported^{19,23}. Making a diagnosis in patients with (possible) IBD can be difficult. The results on the median duration between onset of symptoms and diagnosis can be misleading. This is illustrated by the fact that 31% of the patients with CD and 18% of the patients with UC had complaints for more than a year before a diagnosis of IBD was made. Symptoms at first presentation might give a clue to the diagnosis, but are not specific to IBD and do not differentiate between UC and CD. Rectal bleeding at diagnosis was present in more than 90% in patients with UC. However, this symptom was also observed in 39% of the patients with CD. While weight loss, tiredness and abdominal pain were more frequently reported in CD, these symptoms were also reported in a substantial proportion of patients with UC.

The age and sex distribution in CD is similar to that observed in other recent studies, with a peak incidence at earlier age and higher incidence rates in females than in males^{12,14,16,20}. The higher female incidence in the younger age groups might

be compatible with a role for exogenic risk factors, for example oral contraceptive use and smoking, in the clinical expression of the disease. Another interesting observation is the male predominance in UC in the older age groups. Higher incidence rates in older males have been reported before by some authors but not by others and might, also here, reflect a different exposure to exogenic risk factors^{17,19,24}. The frequently quoted "second peak" in older age categories was neither found in CD nor in UC.

Only about half of the number of patients registered with CD and a quarter of the patients registered with UC were hospitalised during the first six months of their disease. This is low compared to the Ruhr area in Germany, where only 7.8% of patients with CD were diagnosed as outpatients, and urges the question of complete case ascertainment and comparability of incidence rates between different study areas¹⁴. The need for completeness of data in epidemiological studies of IBD is evident. Our results are based on patients seen by specialists at one of the six hospitals in the study area. Strictly speaking this may not be defined as a population-based study. It was our opinion, however, that most of the IBD patients would either be referred to an outpatient department or would have been hospitalised at some time during the first year after diagnosis. It has been suggested that questionnaires to general practitioners are essential to producing accurate estimation of disease incidence⁶. However, results in The Netherlands using questionnaires have been disappointing⁶. The present study used a computerised file of all diagnoses of a limited subgroup of general practitioners, participating in the Registration Network Family Practices to address this item⁹. Because of practical implications, it was impossible to involve all general practitioners working in the study area (more than 300 in number). The size of this subgroup is probably too small to make a valid estimation of completeness of case ascertainment, but the study suggests that most or all of the patients with CD, and most of the patients with e-UC are known at the IBD Registration. Case ascertainment of UP needs improvement.

In epidemiological studies of UC, patients with UP are classified in different ways²⁵. Some authors have excluded such cases from their studies, but most have included them and given the ratio of UP:UC^{17,26-31}. Finally, some authors have grouped them with UC cases affecting part or all of the sigmoid colon³²⁻³⁴. Differences in time trends and certain other epidemiological characteristics (such as age and sex distribution) between UP and extensive UC suggest that UP is a specific disease, the aetiology of which may differ to some extent from that of extensive colitis²⁵. The differences in UC incidence between various regions could be explained by the inclusion of milder cases, particularly UP, another reason to separate both entities³⁵. The incidence rate of UP as found in our study, 2.5 per

100.000 inhabitants and year, is lower than reported in most recently published studies^{12,15,20,24,26,28-31}. Swedish data would even suggest that at least 60% of the total UC cases actually are UP^{24,25}.

In summary, our results suggest a high incidence of IBD in The South Limburg area of The Netherlands. Incidence rates are higher than previously reported in our country and also higher than published by centres of most surrounding countries. When comparing different studies on the incidence of IBD, special attention has to be paid to the diagnostic criteria and the methods of case ascertainment used. Differences in age and sex adjusted incidence rates are possibly compatible with a role for exogenic risk factors. Continuation of studies with prospective and well-defining disease registrations of IBD might contribute to the understanding of the cause(s) of IBD.

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Chapter IV

Familial aggregation of Inflammatory Bowel Disease: a population-based study in South Limburg, The Netherlands

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Incidence of IBD

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Abstract

Background: The aim of our study was to investigate the prevalence of Crohn's disease (CD) and ulcerative colitis (UC) in first-degree relatives of IBD patients, living in a well-defined area.

Methods: IBD patients known at the IBD Registration South Limburg as well as population-controls were asked about the occurrence of IBD in their first-degree relatives.

Results: IBD was reported and confirmed in 16 (out of 1554) relatives by 11 (out of 245) patients. Prevalence of IBD was highest for siblings (1.5%) and children (1.3%) while only 0.2% of the parents were affected with IBD. Among relatives of the control subjects, IBD was observed in 0.8% (vs. 4.5 % in IBD patients), resulting in an odds ratio of 5.7 (95% CI: 2.0-16.7).

Conclusions: The observed risk of IBD for first-degree relatives of IBD patients was higher than in controls. However, the risk in our population is lower than has been reported by other centres, possibly caused by the population-based character of our study.

Introduction

While the aetiology of inflammatory bowel disease is still unknown, there is ample evidence that Crohn's disease (CD) and ulcerative colitis (UC) are in part determined by genetic predisposition¹⁻⁶. This is suggested by studies on familial aggregation of IBD and the finding of a higher concordance rate in monozygotic than in dizygotic twins⁷⁻¹⁰. Several studies have shown an approximate thirtyfold increase in disease prevalence among siblings compared to the community-wide prevalence¹¹. The proportion of IBD patients with a positive family history varies considerably between case series, depending on the studied population, but is usually in the range of 10 to 20%. The aim of the present study was to investigate family aggregation of IBD in a population-based cohort of persons with CD and UC residing in a geographical well-defined area and, secondly, to compare these findings with the occurrence of IBD in population-controls living in the study area.

Materials and methods

Patients

Cases were selected from the South Limburg IBD Registration, an ongoing study on the epidemiology of IBD in a well-defined geographic area in the south east of The Netherlands¹². This study started in 1991. The area has a population of close to 642.000 inhabitants. UC (including chronic proctitis) and CD were defined according to the criteria of Truelove & Witts and Lennard-Jones¹³.

All incident and prevalent cases with UC and CD, registered at the South Limburg IBD Study Centre until June 1994, who were living in the cities of Maastricht or Brunssum at time of registration (during the 1991-1994 period), were eligible to be included in the present study. Maastricht, localisation of the university hospital, is the largest city of South Limburg and Brunssum is a smaller town which has a general district hospital (population size 118.102 and 30.139, respectively). Ethnic or racial minorities are rare in both cities, and the religion of most inhabitants is Roman Catholic.

Whenever two or more members of the same family were registered, only the member in whom CD or UC was first diagnosed was considered as a proband, while the others were regarded as relatives.

Information on family aggregation

A basic questionnaire concerning number and sex of first-degree relatives (parents, siblings and children) and the presence or absence of a positive family history for IBD was applied either by a personal interview, by a telephone interview, or sent by mail. In case of a positive family history, an extended printed questionnaire was completed by the patients, including information on the relative marked as having IBD. Medical information of suspected first-degree relatives was requested and reviewed to verify a diagnosis of IBD, according to the study criteria. Only relatives with sufficient medical information were included in the analyses. The number of relatives, prevalence of IBD among the relatives, and type of IBD were determined.

Controls

Controls were all living in the study area and had no history of IBD. They were recruited in co-operation with the Registration Network Family Practices (RNH), which is a reliable dynamic sampling frame of the Dutch general population¹⁴. Out of 47.750 registered patients at the RNH, a sample of 924 persons was randomly selected. This group received a questionnaire on IBD in their first-degree relatives, which was completed by 616 persons (52% males, median age at time of the questionnaire 37 (13-81) years). Every control was asked about the occurrence of CD, UC or chronic proctitis in either their parents, siblings or children. Because of privacy reasons, only date of birth and sex of the control population were known and verification of the diagnoses of the relatives of controls was not possible.

Statistical analysis

All statistical analyses were performed with SPSS package 6.0 for Windows and the Confidence Interval Analysis program (CIA)¹⁵. Descriptive statistics were provided as median, range and frequencies. Odds ratios (and 95% confidence intervals) were calculated. Prevalence of UC and CD among first-degree relatives was estimated by dividing the number of relatives with either disease by the number of first-degree relatives.

Results

A total of 263 IBD patients, living in Maastricht or Brunssum, were registered until June 1994. Those patients who were deceased ($n=3$), had moved out of the study area ($n=4$), refused to collaborate ($n=2$), or could not be traced by mail or telephone ($n=1$) were categorised and not included in the subsequent analysis. The same procedure was performed in one patient with CD who was adopted to his family. Seven patients were regarded as relatives instead of probands, since a diagnosis of IBD in one of their first-degree relatives was made in advance, resulting in 245 patients who were included in the analysis (**Table 4.1**). In 167 patients a personal interview was performed, 37 were approached by a telephone interview, and 41 by a postal questionnaire and. Of those 132 were classified as CD (67% females, median age 40 (16-81) years, median duration of disease 9 (1-41) years and 113 as UC (49% females, median age 46 (17-81) years, median duration of disease 7 (1-37) years).

Table 4.1 Eligible patients and response to the interview

Eligible patients		
Patients in South Limburg Registry	1991-1994	1171
Patients living in Maastricht or Brunssum	1991-1994	263
Patients not included		18 (7%)
Death		3
Refused		2
Moved away		4
Inability to contact		1
Adopted to family		1
Regarded as relative (instead of proband)		7
Complete responders		245 (93%)
Crohn's disease		132
Ulcerative colitis		113

The family pedigrees of the 245 patients included a total of 1571 first-degree family members; sufficient information was available on 1554 (99%) of them: 485 parents, 756 siblings and 313 children. A positive family history of IBD was reported by 22 (9%) patients (probands), twenty of whom provided information on their relatives. Because some of the probands reported more than one relative, the subsequent analysis included a total of 28 relatives. Eight (29%) were known at the South Limburg IBD Registration and had the disease confirmed from their medical records. Of the remaining 20 relatives, 8 (29%) had disease confirmed from records of their general practitioners, in 9 (32%) an IBD diagnosis according the

Familial aggregation

study criteria could not be established and of three (11%) relatives insufficient information for disease classification was available. A positive first-degree family history could be confirmed in 11 probands (4.5%): 7 patients (5.3%) with CD and 4 patients (3.5%) with UC. Eight patients had one, one patient had two and two patients had three affected family members, resulting in 16 relatives with IBD among the 1554 first-degree relatives, a prevalence of 1.0%. The highest prevalence was observed among siblings (1.5%) and children (1.3%), while only 0.2% of the parents were affected with IBD (Table 4.2). Disease concordance was observed in 88%: 9 cases with CD and 1 with UC among relatives of patients with CD, and 5 cases with UC and 1 with CD among relatives of patients with UC.

Table 4.2 Prevalence of IBD among relatives of 245 IBD patients

Relationship	Total n	Sufficient information n	Affected with CD n (%)	Affected with UC n (%)	Total affected n (%)
First-degree	1571	1554	10 (0.6)	6 (0.4)	16 (1.0)
of UC patients	775	768	1 (0.1)	5 (0.7)	6 (0.8)
of CD patients	796	786	9 (1.1)	1 (0.1)	10 (1.2)
Parents	490	485	1 (0.2)	0	1 (0.2)
of UC patients	226	223	0	0	0
of CD patients	264	262	1 (0.4)	0	1 (0.4)
Siblings	766	756	8 (1.1)	3 (0.4)	11 (1.5)
of UC patients	392	388	1 (0.3)	2 (0.5)	3 (0.8)
of CD patients	374	368	7 (1.9)	1 (0.3)	8 (2.2)
Offspring	315	313	1 (0.3)	3 (1.0)	4 (1.3)
of UC patients	157	157	0	3 (1.9)	3 (1.9)
of CD patients	158	156	1 (0.6)	0	1 (0.6)

Age at time of diagnoses was not significantly different in patients with and without a positive family history (median age 28 (15-66) years and 29 (10-80) years, respectively), and no difference was observed in the median age at time of enrolment (44 (19-71) years and 41 (16-81) years). In addition, no significant difference was found in duration of the disease (median duration 14 (2-37) years and 8 (1-41) years, respectively).

Out of the 616 controls, five persons (0.8%) reported a relative with IBD, all with CD; three in a sibling, one in a child and one in a parent. It was not possible to verify diagnoses in the relatives of the controls, but regarding these patients as truly IBD, the odds ratio for positive family aggregation in IBD patients compared to controls would be 5.7 (95% CI: 2.0-16.7), 4.5 (1.2-17.0) in UC and 6.8 (2.1-21.9) in CD.

Discussion

In this study the main finding is a moderately high frequency of first-degree family members with IBD in a group of unselected IBD patients (5.3% in CD and 3.5% in UC). Much effort has been made to obtain information on all first-degree relatives, resulting in a 98% completeness. In studies with a lower response rate, it is conceivable that a lower rate of familial occurrence among persons not responding may have contributed to the higher rates of familial occurrence in those studied. Since all diagnoses had to be verified according to strict criteria, the reported prevalence of IBD in first-degree relatives of 1.0% is a minimum number. It was remarkable that, compared with the patients' opinion, a positive family history could only be confirmed in 57% of the relatives. This raises doubts as to the results of some previous studies, in which only questionnaires were used to obtain information on IBD diagnoses in relatives¹⁶. We did not include information on second-degree relatives, since it would have been difficult, if indeed possible, to check their medical diagnoses, which would have resulted in less reliable information.

Compared to other recent studies on familial aggregation of IBD, our results on the prevalence of IBD in relatives are lower than most (**Table 4.3**). Crude rates of up to 40% of family IBD history, as well as frequencies of IBD as high as 2% among siblings have been described, but these data probably grossly overestimate the real prevalence. The only Dutch study on familial incidence of CD by Weterman et al.⁶ was published in 1984 and reported a prevalence of 8% in a selected population visiting a referral hospital. Selection bias in the present study was minimised by including all prevalent IBD patients who were living in the well-defined catchment area and who were known at the outpatient clinics of the six hospitals in the study area participating in the South Limburg IBD Registration.

As has been observed before, prevalence of IBD was higher in siblings and children compared to parents¹⁶⁻¹⁸. It is likely that many offspring of patients have not reached the age at which symptoms are manifested, and the risk to offspring is therefore probably underestimated by the majority of studies, including ours¹⁹.

Familial aggregation

Since we had no information on the age of the 1544 relatives, it was impossible to calculate age- and sex- specific prevalence rates or to develop age-corrected empirical risks of IBD, as was done by Yang et al²⁰.

Table 4.3 Family history in first-degree relatives of patients with IBD

Disease (number)	Year of Publication	% positive family history	% siblings with IBD	% parents with IBD	% offspring with IBD	Study area
IBD(838)	1981	16.3	3.1	4.7	-	Cleveland ²⁷
CD (400)	1984	8.0	1.9	1.5	0.6	The Netherlands ⁶
IBD(179)	1986	22.0*	2.6	4.6	1.9	Chicago ³
IBD(188)	1989	17.6	5.2	2.9	2.5	Los Angeles ¹⁶
UC (504)	1991	8.1	1.6**	-	-	Copenhagen ²¹
CD (133)	1991	5.3	1.2**	-	-	Copenhagen ²¹
UC (963)	1987	5.7	-	-	-	Stockholm ²²
CD(1048)	1991	8.9	-	-	-	Stockholm ²³
CD (157)	1991	6.5	1.5	1.0	0	Hadassa ²⁵
IBD(352)	1992	9.9	-	-	-	Pennsylvania ²⁸
IBD(652)	1992	5.5	1.2	0.5	0.4	Northern Italy ¹⁸
CD (433)	1994	11.5	4.2	2.2	0.8	Oxfordshire ²⁹
UC (113)		3.5	0.8	0	1.9	Present study
CD (132)		5.3	2.2	0.4	0.6	Present study

* First and second-degree relatives

** Combined first-degree relatives

The estimated odds ratio for a positive family aggregation in IBD patients compared to controls in our study was lower than reported by others²¹⁻²³. Confirmation of the diagnoses in relatives of patients could only be made in about half of the cases. One has to realise that, in contrast to the cases, an IBD diagnosis as reported by the controls could not be verified because of privacy reasons, which may have resulted in this lower odds ratio.

UC incidence was higher than CD among relatives of UC patients, and vice versa CD among relatives with CD. However, as has been observed in previous studies, both diseases were also observed within the same families with a higher frequency than expected only by chance^{20,24}. This could suggest either an aetiological

relationship or a misclassification of the disease. A positive family history was somewhat greater among relatives of probands with CD, but this difference was not as large as expected from the results of previous studies^{5,11,18,20,22,23,25}.

The age of onset of IBD seems to be correlated with the severity of the disease²⁴. IBD patients with early age of onset have been reported to have an increased positive family history compared to patient populations with a higher age of onset^{1,20,23,26}. UC patients without positive family histories have been reported to be older than UC patients with a positive history. We were not able to confirm this last observation.

In summary this population-based study, including only patients and relatives after confirmation of an IBD diagnosis according to strict criteria, shows one of the lowest prevalence figures reported in first-degree family members. Therefore, in our area patients can be reassured that the risk for family members to develop IBD is relatively low.

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Chapter V

"Modern life" in the epidemiology of Inflammatory Bowel Disease: a case-control study with special emphasis on nutritional factors

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Abstract

Background: The rising incidence of IBD since the Second World War coincides with profound changes of the dietary pattern. The aim of the study was to investigate the possible pathogenic role of some characteristic "modern life" dietary factors in IBD.

Methods: A case-control study was performed, studying risk factors in recently diagnosed cases, 290 with Crohn's disease and 398 with ulcerative colitis, compared to 616 population-controls. Smoking, age, gender, and education were taken into account by using logistic regression analysis.

Results: A positive association with cola drinks (OR: 2.2 (95% CI: 1.5-3.1)), chewing gum (OR: 1.5 (95% CI: 1.1-2.1)), and chocolate (OR: 2.5 (95% CI: 1.8-3.5)) and a negative association with citrus fruit consumption (OR: 0.5 (95% CI: 0.3-0.7)) and the development of Crohn's disease was found. Consumption of cola drinks (OR: 1.6 (95% CI: 1.1-2.3)) and chocolate consumption (OR: 2.5 (95% CI: 1.8-3.5)) was positively associated with developing ulcerative colitis. There was a negative association between the intake of citrus fruits (OR: 0.5 (95% CI: 0.4-0.8)) and 'having a toy pet' for a period longer than five years (OR: 0.6 (95% CI: 0.4-0.9)) and developing the disorder. Moreover was negatively associated with developing ulcerative colitis. No association with the frequency of tooth brushing and developing IBD was found.

Conclusions: All the nutritional items mentioned may be true risk factors, or they just might be the expression of a modern life-style also involving other risk factors for the development of IBD which at the present are still unknown.

Introduction

In the Western world an increase in the incidence of ulcerative colitis (UC) started in the early 1950s and has continued fairly stable for the last 25 years. In Crohn's disease (CD), the most rapid increase in frequency occurred during the period 1965-80, reaching a plateau in recent years¹⁻⁴.

At present the cause(s) of CD and UC are unknown. However, there are strong arguments to suggest that, in addition to a genetic predisposition, environmental risk factors are important in the pathogenesis of Inflammatory Bowel Disease (IBD)^{5,6}. In the industrialized world, the rising incidence of IBD during the last half century coincides with profound changes in environmental factors, especially the dietary pattern. This has led us to investigate the possible pathogenic role of some characteristic "modern life" dietary factors in UC and CD in a case-control study of recently diagnosed patients.

Patients and methods

Cases

All cases studied were non-hospitalized at the time of the investigation and had varying degrees of disease activity. They are participating in the South Limburg Epidemiological Study on Inflammatory Bowel Disease (IBD), an ongoing project on epidemiology, pathogenesis, and clinical course of IBD in the south-east of The Netherlands⁷. The study area has a population of about 642.000 inhabitants, and medical care to IBD patients is provided mainly by specialists working at six hospitals (one university hospital, two general district hospitals, and three local hospitals). Since October 1991, prevalent as well as incident cases of IBD have been reported by the specialists to the IBD study centre. All patients received a mailed questionnaire within a period of six months after they had given informed consent for data collection. Medical data were subsequently collected from the medical records.

The criteria of Lennard-Jones were applied in case definition for CD and those of Truelove & Witts for UC⁸.

Using all the available medical information obtained during the first six months after diagnosis, location of the disease in the large and small bowel was carefully recorded. CD was subdivided into exclusive small bowel disease, exclusive colonic disease, and combined small and large bowel disease. UC was subdivided into ulcerative proctitis (UP) and extended ulcerative colitis (e-UC), depending on whether or not the disease extended proximal to the rectosigmoidal junction. In e-UC a further difference between left-sided colitis (inflammation up to, but not

dental care characteristics were asked (denture (yes/no), fillings (yes/no), and the frequency of teeth brushing during both periods).

Statistical analysis

Descriptive statistics are provided as median with 25 and 75 percentiles in brackets and frequencies with percentages in brackets. The entire group of controls was used for both series of cases. The odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were estimated by multiple logistic regression analysis with dummy variables indicating the different categories of potential confounders. Four separate analyses were performed: consumption before complaints and present consumption in CD and in UC respectively. Age at time of the questionnaire, gender, education, smoking, and oral contraceptive use were all taken into account in the equation. All statistical analyses were performed with the SPSS package 6.0 for Windows. P-values less than 0.05 were considered as being statistically significant.

Results

Between October 1991 and July 1996, a total number of 1463 patients were reported to the study centre with a diagnosis of either UC or CD according to the study criteria. After a maximum of two reminders 1355 (93%) cases of IBD (687 patients with UC and 668 patients with CD) responded to the questionnaire. Of this group of 1355 patients 417 (31%) were newly-diagnosed whereas the others were already known with IBD before the start of the registration. A total of 688 (51%) patients (290 with CD and 398 with UC), reporting the first complaints within 5 years from receiving the questionnaire, were subsequently selected for the present study. Mapping of disease location was available of 248 (86%) patients with CD and of 342 (86%) patients with UC. In the control group the questionnaire was completed by 616 persons (67%), who were all included in the analysis. The demographic characteristics of both groups are presented in **Table 5.1**.

Table 5.1 Demographic characteristics of patients and controls

	controls	Crohn's disease	ulcerative colitis
Number	616	290	398
*Age at first complaints / in 1987** (controls)	30 (22-44)	27 (21-38)	36 (27-51)
*Age at diagnosis	-	28 (21-38)	36 (27-51)
*Age at questionnaire	37 (29-51)	29 (24-40)	39 (30-54)
Gender (% female)	48	57	43
Educational level			
low (%)	30	39	32
middle (%)	38	35	43
high (%)	32	26	25
Disease location			
small bowel only nr(%)		71 (25)	
large bowel only nr(%)		37 (13)	
small and large bowel nr(%)		149 (48)	
proctitis nr(%)			61 (15)
left-sided colitis nr(%)			177 (45)
pancolitis nr(%)			104 (26)

* median (25-75 percentiles)

** 1987 in controls replaces the year of first complaints in cases

Smoking and oral contraceptive use

Accurate data on smoking history and present status were available in 99% of the patient group and 97% of the control population. The estimated odds ratios were derived from the multiple logistic regression analyses and are shown in Table 5.2. Compared to controls, CD patients were more likely to be smokers before the first complaints of IBD and also after the diagnosis had been made at the time of the questionnaire. The risk of developing UC was highest in patients who had stopped smoking before the first complaints, but never-smokers also had a higher risk of developing the disease. At the time of the questionnaire UC patients were less likely to smoke than controls.

No significant difference was observed between controls and patients with either disease concerning the use of oral contraceptives.

Table 5.2 Smoking and oral contraceptive use in patients and controls

	controls %	Crohn's disease %	OR (95% CI)*	ulcerative colitis %	OR (95% CI)*
Non-smokers at first complaints / in 1987**	41	36		39	
Smokers at first complaints / in 1987**	41	50	1.5 (1.0-2.2)	21	0.4 (0.3-0.6)
Ex-smokers at first complaints / in 1987**	18	14	1.4 (0.8-2.3)	39	2.4 (1.6-3.5)
Present smokers (questionnaire)	32	46	1.6 (1.2-2.3)	15	0.3 (0.2-0.4)
Oral contraceptive use ever (% of females)	81	86	1.2 (0.4-3.1)	82	1.2 (0.6-2.4)

* Logistic regression estimated odds ratios, adjusted for age, gender and educational level

** 1987 in controls replaces the year of first complaints in cases

The significant finding of the selected nutritional items are presented in **Table 5.3** for CD and in **Table 5.4** for UC.

Selected nutritional items before complaints

A positive association of the consumption of chocolate, cola drinks, and chewing gum, and a negative association of the consumption of citrus fruits before the first complaints was found with CD (**Table 5.3**). After dividing the group into non-smokers (including ex-smokers) and smokers before the first complaints, the odds ratios changed slightly: in non-smokers the odds ratios to develop CD were for chocolate 3.2 (95% CI: 1.9-5.4), for cola drinks 2.5 (95% CI: 1.4-4.3), for chewing gum 1.7 (95% CI: 1.0-3.0), and citrus fruits 0.7 (95% CI: 0.4-1.2). The corresponding odds ratios in smokers at first complaints were: chocolate 2.0 (95% CI: 1.2-3.4), cola drinks 2.0 (95% CI: 1.2-3.4), chewing gum 1.2 (95% CI: 0.7-2.1), and citrus fruits 0.7 (95% CI: 0.5-1.2) respectively.

As shown in **Table 5.4**, the consumption of cola drinks and chocolate consumption was positively associated with developing UC. There was a negative association between the intake of citrus fruits and developing the disorder. Moreover 'having a toy pet' for a period longer than five years was negatively associated with developing UC. In the group of non-smokers at the time of first complaints the odds ratios of developing UC were for chocolate 3.0 (95% CI: 1.9-4.4), for cola drinks 1.8 (95% CI: 1.1-2.7), for citrus fruits 0.7 (95% CI: 0.5-1.1), and for

'having a toy pet' 0.5 (95% CI: 0.3-0.8). The corresponding odds ratios in smokers at first complaints were: chocolate 1.5 (95% CI: 0.9-2.9), cola drinks 1.7 (95% CI: 0.8-3.2), citrus fruits 1.0 (95% CI: 0.5-2.0), and having a toy pet 1.2 (95% CI: 0.6-2.4) respectively.

Selected nutritional items at the time of the questionnaire

To investigate whether the consumption pattern of the selected items had changed over time, we also asked the patients to report their current intake. In CD (Table 5.3) the association with chocolate and chewing gum was no longer observed, whereas cola drinks were still significantly more often reported by patients, although the calculated odds ratio was lower than before the first symptoms 1.4 (95% CI: 1.0-2.0). The negative association with citrus fruits at the time of the questionnaire 0.4 (95% CI: 0.2-0.5) was comparable with the findings of the period before the first complaints. Coffee (with or without sugar) was consumed less often at the time of the questionnaire, and, on the other hand, tea with sugar more frequently.

At the time of the questionnaire, three nutritional items were significantly associated with having UC (Table 5.4): a positive association for chocolate consumption 1.8 (95% CI: 1.3-2.4), and a negative association for both citrus fruits intake and coffee (with or without sugar) drinking.

Disease location and risk factors

In 84% of the patients with CD adequate mapping of disease location was available. With respect to disease location, the positive association between consumption of cola drinks, chocolate and chewing gum before first complaints was highest in isolated small bowel disease with odds ratios of 3.2 (95% CI: 1.4-7.6), 3.3 (95% CI: 1.4-7.5), and 2.2 (95% CI: 0.9-5.2) respectively. The negative association with citrus fruits was only significant in patients with isolated colonic disease: 0.4 (95% CI: 0.2-0.7). A remarkably strong association between stopping smoking before complaints and isolated colonic disease was observed with an odds ratio of 3.1 (95% CI: 1.4-6.9).

In UC, where adequate mapping was also available in 84% of the patients, the positive association with chocolate consumption before the first complaints was observed in all subgroups with comparable odds ratios, whereas the positive association with cola drinks, and the negative association with citrus fruits and 'having a toy pet' longer than five years was only significant in the largest subgroup with left-sided colitis. Finally, a positive association was observed in the pancolitis group with breastfeeding 2.0 (95% CI: 1.0-3.9).

Table 5.3 Consumption pattern in Crohn's disease compared to controls before the first complaints and at the time of the questionnaire of selected nutritional items

	Before first complaints		At time of questionnaire	
	patients number (%)	controls number (%)	patients number (%)	controls number (%)
Chocolate				
none or one per week	99 (34)	379 (63)	171 (60)	406 (67)
more than once weekly	188 (66)	223 (37)	115 (40)	198 (33)
				1.2 (0.9-1.7)
Cola drinks				
none or one per week	94 (34)	386 (64)	146 (53)	408 (69)
more than once weekly	183 (66)	216 (36)	128 (47)	186 (31)
				1.4 (1.0-2.0)
Chewing gum				
none or one per week	93 (34)	341 (56)	128 (47)	357 (60)
more than once weekly	184 (66)	264 (44)	147 (53)	241 (40)
				1.3 (0.9-1.9)
Citrus fruits				
none or one per week	84 (30)	151 (25)	114 (40)	126 (21)
between 2 and 5 weekly	153 (54)	282 (47)	122 (43)	265 (45)
more than 5 weekly	37 (16)	164 (28)	47 (17)	205 (34)
				0.4 (0.2-0.5)**
Coffee				
no coffee	29 (11)	87 (15)	59 (22)	47 (8)
once or more daily	247 (98)	498 (85)	214 (78)	529 (92)
				0.5 (0.3-0.8)
Tea with sugar				
no tea with sugar	139 (53)	319 (63)	128 (49)	315 (63)
once or more daily	423 (47)	187 (37)	133 (51)	183 (37)
				1.6 (1.2-1.5)

* Multiple logistic regression estimated Odds Ratios adjusted for smoking, gender, age, educational level, and selected nutritional factors

** For combined categories citrus fruits more than once weekly

Table 5.4 Consumption pattern in ulcerative colitis compared to controls before the first complaints and at the time of the questionnaire of selected nutritional items

	Before first complaints		At time of questionnaire	
	patients number (%)	controls number (%)	patients number (%)	controls number (%)
Chocolate				
none or one per week	171 (44)	379 (63)	223 (60)	406 (67)
more than once weekly	217 (56)	223 (37)	157 (40)	198 (33)
				1.8 (1.3-2.4)
Cola drinks				
none or one per week	190 (51)	386 (64)	238 (53)	408 (69)
more than once weekly	181 (49)	216 (36)	129 (47)	186 (31)
				1.2 (0.8-1.6)
Citrus fruits				
none or one per week	105 (27)	151 (25)	128 (40)	126 (21)
between 2 and 5 weekly	219 (56)	282 (47)	188 (43)	265 (45)
more than 5 weekly	65 (17)	164 (28)	70 (17)	205 (34)
				0.3 (0.2-0.4)
Coffee				
no coffee	43 (11)	87 (15)	57 (22)	47 (8)
once or more daily	338 (89)	498 (85)	325 (78)	529 (92)
				0.5 (0.3-0.9)
Toy pet				
shorter than 5 years	228 (73)	341 (67)	-	-
longer than 5 years	84 (27)	170 (33)	-	-
				0.6 (0.4-0.9)

* Multiple logistic regression estimated Odds Ratios adjusted for smoking, gender, age, educational level, and selected nutritional factors

Non-significant findings

Oral contraceptive use, breastfeeding, and the use of an artificial nipple were not associated with the development of IBD, as were the consumption of fish, preserved food consumption, the daily number of cups of coffee and, orange juice, and sweets. None of the dental care characteristics addressed in our survey was significantly associated with developing either CD or UC.

Discussion

There is no doubt that in the Western world nutritional habits have changed over the past decades. In the same period the incidence of CD and UC have increased. Food is a major factor affecting the intestinal environment, and the considerable change in dietary habits may explain why IBD has become more frequent. To investigate nutrition as a possible risk factor for the development of IBD, some typical modern life nutritional items were selected for the present study.

The major finding of the present study was a greater risk for CD among those with a high consumption of chocolate, chewing gum, and cola drinks, whereas a decreased risk was observed with a high intake of citrus fruits. Except for chewing gum, the consumption of these food items was also associated with the development of UC.

What is the common denominator of the selected nutritional items implicated? In Europe, the consumption of chocolate, cola drinks and chewing gum has steadily increased since the Second World War, and might be regarded as a typical modern life-style living habit. Overall, the intake of citrus fruits also has increased during the same period. However, a relatively low intake of citrus fruits might correspond to a life style based on concentrated carbohydrates and fat. In line with this view, the group of Persson et al. has reported a positive association with fast food consumption and IBD¹⁰. The authors stated that eating fast-food probably defined a life-style rather than the consumption of specific foods and drinks. An interesting study from Japan, examining the correlation between the rise of the incidence of CD and parallel changes of dietary habits, showed that the rapidly rising incidence of CD in that country was strongly correlated with increased dietary fat intake¹¹. In the opinion of the authors, the composition of the fat intake, high in (n-6) fatty acids and relatively low in (n-3) fatty acids, was of importance with regard to the pathogenetic mechanism. This interesting finding has yet to be confirmed by other studies.

Chocolate, cola drinks and chewing gum all share a high sugar content. Previous studies have consistently found strong positive associations between sweetened foods and IBD¹²⁻¹⁹. This might be interpreted as a consequence of the disease rather

than a factor in its pathogenesis. Refined sugar is rapidly absorbed in the small intestine and has no bulking effect. Patients may increase the consumption of sugar at an early stage of the disease in an attempt to compensate for loss of energy or weight. However, a causal relationship between long-term increased consumption of refined sugar and the pathogenesis of CD could be explained by a change in the intestinal bacterial flora, potentially leading to intestinal mucosal damage¹⁴.

A decreased consumption of fruit, as was found in our study concerning citrus fruits, has inconsistently been reported in IBD^{14,20-22}. Also here it can be argued that before diagnosis patients with IBD modified their diet in an effort to overcome symptoms of subacute obstruction, weight loss and loose stool²³. Therefore it is of great importance to investigate the pre-illness diet. This was the reason for asking the patients to provide information on the consumption pattern before the first complaints of their bowel disease.

In an effort to reduce recall bias, only newly and recently diagnosed patients were included, limiting the dietary recall period to five years and taking as a cut-off limit the start of complaints according to the patient's view rather than the date of diagnosis. Both retrospective and current dietary questioning are likely to cause some misclassification with regard to food consumption during the relevant period of time in the past²⁴. The so called 'rumination bias' (cases doing more efforts to remember past habits than controls, leading to differential misclassification) is difficult to rule out in studies investigating dietary habits before symptom onset. Whereas we have no reason to believe that patients would over-report their dietary intake in comparison with controls in the present study, it remains difficult to prove the absence of over-reporting of consumption in cases compared to controls. To gain more knowledge on the direction of possible changes in the consumption pattern, we have recorded the dietary habits at the time before the first complaints as well as the present consumption pattern. The present intake of chocolate, cola drinks and use of chewing gum in patients changed with regard to that of controls. However, also at the latter time point a higher intake was still noted in the patient group.

As has been consistently reported before, smoking was positively associated with CD, whereas non-smoking and stopping smoking both were associated with UC. Smoking as a possible confounder was adjusted for by using multiple logistic regression as was done with age, gender and educational status²⁵⁻²⁹. In a second analysis, we investigated the odds ratios in never-smokers and in the group who smoked or had smoked separately, leading to basically the same results. Others have found that smoking and increased sugar intake are separate but also interactive risk factors in CD¹⁷.

No significant differences were found concerning the use of oral contraceptives, another factor reported to be associated with IBD³⁰.

A negative association with coffee consumption at time of the questionnaire was

observed in both CD and UC and a positive association with sugared tea in CD. These findings were only observed after the diagnosis of IBD and should probably be regarded as consequences of the disease rather than factors in the pathogenesis of IBD. A negative association with coffee consumption has been reported before, but other studies have shown no marked different association between cases and controls and even a positive association has been reported^{10,14,22,31-33}.

A striking finding was a decreased risk of UC in patients having had a toy pet for a period longer than five years. Based on the small number of exposed subjects, the significance of this result might be explained by a minimal differential misclassification. However, we have no reason to believe that only the cases have underreported this peculiar item. Originally, this item was included in the questionnaire to investigate a possible (positive) association with CD in the view of increased ingestion of foreign material, which hypothetically might lead to the formation of granulomas in the bowel³⁴. However, in this study having a toy pet longer than five years as a child appeared to be less frequent in non-smokers who subsequently developed UC. It might be speculated that smoking is a substitute for having a toy pet at child age, but we realize that we enter a vague area of explanation.

In the present study cases were identified occurring in a well-defined population. A random sample from the same population was selected as controls. This is in contrast to most case-control studies investigating diet in IBD, which have used patients with other diagnoses as controls (hospital controls)³⁵. Hospital controls are mostly diseased people, and the chance exists that their disease is associated with the exposure under study, in which case they do not constitute an appropriate control series. Since age and gender of the controls were not perfectly matched in the design of the present study, we adjusted in the analysis for both as well as for educational status.

To elucidate whether risks were related to a specific disease location, subgroup analysis also under this aspect was performed. In this calculation the number of patients included in each analysis is low, resulting in wider confidence intervals and possibly masking true associations. The highest odds ratios for chocolate, cola drinks, and chewing gum were observed in small bowel CD, which corroborates the findings of Persson et al. concerning the intake of sucrose in this subgroup¹⁰. A remarkable finding was the positive association of stopping smoking and Crohn's colitis, supporting the hypothesis that smoking protects the colon from inflammation in both subgroups of IBD²⁷.

Because of the previously reported positive association with refined sugar consumption and CD, we included some questions on dental care in the questionnaire. The higher consumption of sugar, if present at all, seemed not to have caused more frequent use of dentures or dental prostheses by patients than by controls. Secondly, the interesting and much debated hypothesis on the relation

between the use of toothpaste and CD, as reported by Sullivan, was investigated³⁶⁻³⁸. No association was found between the presence of CD concerning the frequency of teeth brushing either before the first complaints or after the diagnosis had been made.

In summary, in this case-control study some distinct nutritional factors were found to be associated with IBD: the consumption of cola drinks, chocolate and chewing gum were all positively associated with the development of CD and the former two also with the development of UC in comparison with the controls. The investigated items with high odds ratios reflect a different consumption pattern preceding the rise in incidence of CD and UC. A decreased use of citrus fruits was found to be a risk factor in the development of IBD. All the nutritional items mentioned may be true risk factors, or they might merely be the expression of a modern life-style also involving other risk factors for the development of IBD which at the present are still unknown. An ongoing study, restricted to newly-diagnosed IBD patients, pairwise matched with controls, will, we hope, provide more insight into the relevance of the findings presented³⁹.

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Chapter VI

Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study

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Abstract

Background/Aims: To elucidate the role of appendectomy in Inflammatory Bowel Disease (IBD) a case-control study was performed in a well-defined population.

Methods: Seven years' prevalent and 3.5 years' incident cases with IBD, registered in South Limburg, The Netherlands, were separately studied. Controls were age- and sex-matched subjects from the same population.

Results: In 232 prevalent ulcerative colitis (UC) cases the risk of developing UC was significantly lower after previous appendectomy (OR: 0.36 (95% CI: 0.15-0.80)); subgroup analysis found a protective effect only in pancolitis (OR: 0.2 (95% CI: 0.02-0.7)). In 208 patients with Crohn's Disease (CD) the odds ratio was not significantly increased, but a positive association with appendectomy was observed in ileocolic disease. A significant larger proportion of appendectomies was performed close to the time of diagnosis. Smoking was not a confounding factor. No statistically significant associations were observed in incident IBD patients. Prevalent and incident patients taken together resulted in odds ratios of 0.44 (95% CI: 0.24-0.78) in UC and 1.65 (95% CI: 0.96-2.91) in CD.

Conclusions: An overall protective role of appendectomy for UC was observed; however, this was only significant in the prevalent patient group. The observations in CD suggest that appendectomy in some cases was due to still undiagnosed CD. The fact that sex- and age- matched population-controls were used in this study may contribute to a less pronounced association between appendectomy and UC than recently reported by others.

Introduction

The aetiology of ulcerative colitis (UC) and Crohn's disease (CD) is unknown. There is evidence for an intense and prolonged local mucosal immune response, associated with recruitment and activation of lymphocytes and macrophages¹. The factor(s) triggering this response is (are) presently unknown, but there are strong indications that inflammatory bowel disease (IBD) should be regarded as a multifactorial disease, involving an interaction between genetic and environmental factors, that give rise to an inadequate immunological response^{2,3}.

Recently the role of appendectomy in the pathogenesis of IBD has been discussed. At present, four fully published studies have shown a negative association between appendectomy and UC⁴⁻⁷. The biological explanation for this association is unclear. Factors predisposing for appendicitis may protect against UC, or removal of the appendix may alter the immune response of the gut, making the development of UC less likely.

The relationship between appendectomy and CD was investigated in three of the studies⁴⁻⁶. In two studies a positive correlation between appendectomy and CD was observed, but no data were given on the time interval between the surgical procedure and IBD diagnosis^{4,5}.

Patient as well as control selection has varied widely in the preceding studies. To further elucidate the suggested relations between appendectomy and the development of IBD, a case-control study was carried out in The Netherlands. To evaluate whether the results depend on the prevalence or incidence status of the cases, we separately analyzed the data of prevalent cases as well as of a group of newly-diagnosed incident patients with either UC or CD.

Patients and methods

Patients all lived in the South Limburg area, located in the south-east of The Netherlands, and were diagnosed as having either UC or CD according to the definitions of Truelove & Witts and Lennard-Jones⁸. On January 1 1991, the region had a population of 638.781. There are six hospitals (five general district hospitals and one university hospital) situated in the study area. From October 1991 onwards, specialists working in these hospitals were asked to report all their patients with inflammatory bowel disease to the South Limburg IBD Study Centre, as part of an ongoing study on the prevalence and incidence of IBD in this area.

In the present study, two analyses were performed: the first of all prevalent patients until January 1 1991, who were diagnosed since January 1984 and the second of a group of incident cases with UC and CD registered at the IBD Study Centre from January 1991 until November 1994, who had been diagnosed between

January 1991 and September 1994. The overall odds ratios in combined prevalent and incident patients with UC and CD were subsequently calculated. After the written informed consent of the patients had been obtained, additional medical data on disease characteristics and localization of inflammation were collected from the medical charts and subsequently the diagnoses were verified according to the study criteria by a panel of senior gastroenterologists.

The controls were all living in the study area and had no history of IBD. They were recruited in cooperation with the Registration Network Family Practices (RNH), which is a reliable dynamic sampling frame of the Dutch general population⁹. Out of 47.750 registered persons at the RNH, a sample of 936 persons, with no record of having IBD, were randomly selected.

Complementary data were obtained by a postal questionnaire. In this questionnaire the patients and controls were asked about their smoking status and whether an appendectomy had been performed, and -if so- at what date. When it was not evident whether the appendectomy had been performed before or after the diagnosis of IBD was made, the patients were approached for more detailed information by a second questionnaire or by telephone.

Subsequently, for both analyses, two matched control groups were established, one for UC and the other for CD, by randomly drawing, via a computerized matching program, one control of the same sex and age (± 2 years) for each case.

Since the aim of our study was to investigate the relation between appendectomy and risk of IBD, we ignored any appendectomy in a case performed after the diagnosis of IBD, as well as appendectomies in controls after the date of IBD diagnosis of the matched case.

Statistics

Statistical analyses were performed with SPSS package 6.0 for Windows and the Confidence Interval Analysis program (CIA)¹⁰. Descriptive statistics are provided as median, range and frequencies. Odds ratios (and the 95% confidence interval) were calculated in a pairwise-matched analysis. Smoking was controlled for by logistic regression analysis. In both patient groups a Trend Test was used to compare intervals between appendectomy and IBD diagnosis, and the occurrence of an appendectomy in each disease localization was compared by the Mantel-Haenszel χ^2 method. P-values less than or equal to 0.05 were considered as statistically significant.

Results

The response rate of registered IBD cases to the questionnaire in the prevalent group was 90%, resulting in 441 patients (out of 490) with IBD according to the chosen diagnostic criteria. Of those, 232 patients were classified as UC and 209 patients as CD. In the control group the response rate was 64%, resulting in 602 (out of 936) persons. Matches were found for all cases, except for one patient with CD.

The response rate of IBD cases to the questionnaire of the incident patients was 89%, resulting in 328 patients (out of 368) with UC (n=191) or CD (n=137), respectively. Also here, matched controls were found for all UC patients and for all but one of the CD patients. Overall, a second questionnaire was sent to 105 patients and 3 were approached by phone. Patient characteristics of both groups and of the matched controls are illustrated in **Table 6.1**.

Table 6.1 Patient characteristics of ulcerative colitis (UC) and Crohn's disease (CD) cases and their respective controls after the matching procedure in the prevalent and incident patients with IBD

	UC	UC-Controls	CD	CD-Controls
PREVALENT CASES AND MATCHED CONTROLS				
Number	232	232	208	208
Sex (% males)	56	56	43	43
Median Age (range)	40 (17-80)	42 (18-81)	32 (14-77)	34 (15-75)
% Current smokers	14	33	49	35
Number of patients with appendectomy (%)	9 (4)	25 (11)	27 (13)	16 (8)
INCIDENT CASES AND MATCHED CONTROLS				
Number	191	191	136	136
Sex (% males)	57	57	42	42
Median Age (range)	38 (14-81)	39 (15-81)	30 (13-79)	31 (13-78)
% Current smokers	17	30	44	30
Number of patients with appendectomy (%)	12 (6)	19 (10)	12 (9)	8 (6)

As to the prevalent patient group, the frequency of appendectomies in UC was 4% compared to 11% in the control group. In CD, appendectomy before IBD diagnosis had been carried out in 13% compared to 8% in the control group. When only

Appendectomy

incident cases were analyzed, the difference between cases and controls concerning the frequency of appendectomy were smaller for both disease entities (**Table 6.1**). Pairwise matched analysis resulted in odds ratios of 0.36 (95% CI: 0.15-0.80) in UC and 1.73(95% CI: 0.88-3.52) in CD in the prevalent group, compatible with a protective effect of appendectomy in UC and the opposite trend in CD. When only incident cases were analyzed, the odds ratios were slightly different: 0.56 (95% CI: 0.22-1.35) in UC and 1.50 (95% CI: 0.56-4.23) in CD, both not significant (**Table 6.2**). In the combined group of prevalent and incident patients a protective effect was observed in UC (odds ratio: 0.44 (95% CI: 0.24-0.78)), whereas no significant difference in appendectomy rate between cases and controls was found in CD (odds ratio 1.65 (95% CI: 0.96-2.91)).

Table 6.2 Pairwise matched analysis of appendectomy status in ulcerative colitis and Crohn's disease, subdivided into prevalent and incident patients, both with their sex- and age-matched controls

	Case / control exposure status*				Odds ratio (95% CI)
ULCERATIVE COLITIS					
	P- / C-	P+ / C-	P- / C+	P+ / C +	
prevalent cases	198	9	25	0	0.36 (0.15-0.80)
incident cases	163	9	16	3	0.56 (0.22-1.35)
total group	361	18	41	3	0.44 (0.24-0.78)
CROHN'S DISEASE					
	P- / C-	P+ / C-	P- / C+	P+ / C +	
prevalent cases	166	26	15	1	1.73 (0.89-3.52)
incident cases	116	12	8	0	1.50 (0.56-4.23)
total group	282	38	23	1	1.65 (0.96-2.91)

* Exposure status: P-: patients without appendectomy; P+: patients with appendectomy;
C-: controls without appendectomy; C+: controls with appendectomy

The interval between appendectomy and time of IBD diagnosis in cases, and the interval between appendectomy of a control and date of IBD diagnosis of the matched in both groups is shown in **Table 6.3**. When comparing CD cases with

matched controls, the procedure was carried out significantly more often close to the CD diagnosis in the prevalent group ($p < 0.05$). This was not so in prevalent UC cases compared to controls, nor in incident patient with both diagnoses.

Except in one patient with UC and 9 patients with CD, review of the medical data of the patients allowed full classification of disease extent of all patients. A risk analysis per stratum did not show any significant differences in appendectomy rate in the incident patients (Table 6.4). In prevalent UC patients with pancolitis appendectomy was negatively associated with colitis (odds ratio: 0.2 (95% CI: 0.02-0.7)), whereas a non-significant trend in the same direction was found in proctitis and left-sided colitis. A significant positive association between appendectomy and CD was observed in prevalent patients with combined small and large bowel disease (odds ratio: 4.2 (95% CI: 1.4-17.3). When the prevalent and incident groups were analyzed together, the results in the subgroups according to disease localization were basically the same as those in the prevalent groups of UC and CD.

Table 6.3 Interval between appendectomy and date of diagnosis in appendectomy positive patients of prevalent and incident patients with ulcerative colitis (UC) and Crohn's disease (CD), both with their sex- and age- matched controls

Years before IBD diagnosis	UC Patients number	UC Controls number	CD Patients number	CD Controls number
PREVALENT CASES AND MATCHED CONTROLS				
0-1 years	0	0	5	0
2-5 years	0	0	5	0
>5 years	9	25	17	16
INCIDENT CASES AND MATCHED CONTROLS				
0-1 years	0	0	2	0
2-5 years	2	0	1	0
>5 years	10	19	9	8

Smoking

Current cigarette smoking was observed less frequently in UC (14% smokers in the prevalent and 17% in the incident group) and more frequently in CD (49% and 44% smokers, respectively) compared to the control groups (between 30% and 35% smokers in the four control groups). In UC the odds ratio of current smoking

in patients compared to controls was 0.32 (95% CI: 0.20-0.52) in the prevalent and 0.47 (95% CI: 0.29-0.76) in incident patients. In CD the comparable odds ratios were 1.89 (95% CI: 1.27-2.81) in prevalent and 1.86 (95% CI: 1.12-3.06) in incident patients. Controlling for smoking status did not significantly change the odds ratios for appendectomy as a risk factor in both diseases and in both study groups.

Discussion

In the present study appendectomy was not as uncommon in patients with UC as could be expected in view of the results of four preceding case-control studies. With regard to prevalent patients in this study, the odds ratio of the matched analysis pointed towards a protective role of the procedure against UC. A significant association was only found in patients with pancolitis, however, the numbers in the subgroups are probably too small to allow a stratified risk analysis. In the incident patients with UC the difference between patients and controls was not significant.

Basically the same phenomenon, but in the opposite direction, was seen in CD patients: the odds ratio in the prevalent cases was higher than the odds ratio in the incident patients, although, both failed to reach statistical significance. Subgroup analysis however revealed a statistically significant positive association between CD and appendectomy in the prevalent group with combined small and large bowel CD. A substantial part of appendectomies in CD cases was performed relatively close to the date of diagnosis, which could mean that some of these patients were operated on because of bowel complaints related to CD still undiagnosed at that moment. The observation that mainly combined small and large bowel CD (including ileocecal location) was associated with appendectomy, also supports this view.

Gilat et al., studying childhood factors in relation to inflammatory bowel disease, were the first to report a negative association between appendectomy and UC and a positive association in CD patients⁴. This observation was confirmed for UC, but not for CD, by a case control study in the United Kingdom⁵. The issue of appendectomy as a protective factor in UC has been specifically addressed in two recent studies, both reporting a significant negative association^{6,7}.

The negative association between appendectomy and UC in the present study is less pronounced than reported before (as illustrated in **Table 6.5**) and was not significant in the incident group under study. How can this difference be explained? Many factors have to be taken into account in case-control studies: the choice of cases, the diagnostic classification, selection of controls, the matching procedure, bias and confounding might all influence the results.

Table 6.4 Appendectomy status per localization in prevalent and incident patients

Disease extent	All patients number (%)	Appendectomy number (%)	OR (95% CI)*	All patients number (%)	Appendectomy number (%)	OR (95% CI)*	Combined group OR (95% CI)**
	Prevalent UC patients			Incident UC patients			Total UC
Proctitis	43 (19)	3 (7)	0.8 (0.1-4.4)	49 (26)	3 (6.1)	0.3 (0.01-4.2)	0.6 (0.25-1.5)
Leftsided colitis	112 (48)	4 (3.7)	0.4 (0.1-1.6)	88 (46)	6 (6.8)	0.6 (0.2-1.9)	0.5 (0.2-0.9)
Pancolitis	76 (33)	2 (2.6)	0.2 (0.02-0.7)	54 (28)	3 (5.5)	0.8 (0.1-4.4)	0.3 (0.1-0.9)
	Prevalent CD patients			Incident CD patients			Total CD
Small bowel	30 (15)	5 (16.6)	1.7 (0.3-10.7)	30 (22)	2 (6.7)	0.7 (0.6-5.8)	1.8 (0.7-4.3)
Large bowel	46 (23)	4 (8.7)	0.6 (0.1-2.3)	35 (26)	3 (8.6)	1.5 (0.2-18.0)	1.3 (0.5-3.0)
Combination	124 (62)	18 (14.5)	4.2 (1.4-17.3)	70 (52)	7 (10)	2.3 (0.6-14.0)	2.0 (1.1-3.6)

*: pair wise matched analyses; **: unmatched analyses

Table 6.5 Overview of published studies on appendectomy (A+) frequencies (percentages) and odds ratios (95% Confidence Interval) in ulcerative colitis, Crohn's disease and control groups. Different study designs have been used by the authors.

Author	A+ in patient	A+ in control	OR (95% CI)	A+ in patient	A+ in control	OR (95% CI)
	Ulcerative colitis			Crohn's disease		
Gilat ⁴	4 of 133 (3)	27 of 266 (10)	0.2 (0.1-0.8)	40 of 247 (16)	52 of 494 (11)	1.6 (1.1-2.6)
Gent ⁵	9 of 220 (4)	32 of 220 (15)	0.3 (0.1-0.6)	14 of 130 (11)	10 of 130 (8)	1.4 (0.6-3.4)
Smithson ⁶	7 of 197 (4)	26 of 243 (11)	0.3 (0.1-0.7)	11 of 117 (9)	26 of 243 (11)	0.9 (0.4-1.8)
Rugeerts ⁷	1 of 174 (<1)	41 of 161 (26)	0.02 (0.002-0.8)	-	-	-
Present study	21 of 423 (5)	44 of 423 (10)	0.4 (0.2-0.8)	39 of 344 (11)	24 of 344 (7)	1.7 (1.0-2.9)

Cases in the present study consisted of all registered IBD patients diagnosed between 1984 and 1994 in South Limburg who had completed a patient questionnaire in a very high percentage. Some of the previous studies, mainly using patients attending the outpatient department of -sometimes- tertiary referral-hospitals, probably included a higher number of more severe cases. A recent study on the completeness of the South Limburg Register on incidence of IBD suggested a completeness of 80% in extensive UC and 100% in CD, while patients with proctitis were more frequently underreported (accepted for publication *Dis Colon and Rectum*).

The different results between the prevalent and incident groups analyzed in the present study are possibly due to a selection bias. To be registered as a prevalent patient, cases diagnosed before 1991 had to attend the outpatient department of one of the six participating hospitals after the start of the study in 1991 for one reason or the other. This may underestimate the number of silent cases. Selection will therefore be higher in the prevalent group than in the incident group of patients. Moreover, it cannot be excluded from our data that a time trend in appendectomy rate is responsible for the differences between both groups. However, data on the frequency of appendectomies in The Netherlands during the study period are not in favor of the latter hypothesis (Source: SIG, Information Centre for Health Care, The Netherlands). Finally, one cannot formally exclude a false negative finding due to an insufficiently powered observation, since the number of patients in the incident groups was somewhat less than prevalent cases.

Another difference between the present and other studies is the choice of controls. Three basic tenets of comparability underlie attempts to minimize bias in control selection: the principles of study base, deconfounding and comparable accuracy¹¹. In the present study controls were recruited from persons registered at the general practitioners' offices of the Registration Network Family Practices (RNH)⁹. In The Netherlands almost everyone, regardless of the presence of any illness, is registered with a general practitioner. The RNH is a reliable dynamic sampling frame of the Dutch general population⁹. In this way cases and controls are representative of the same study base (the set of persons in which diseased subjects become cases)¹².

As is illustrated in **Table 6.5**, the preceding studies, all using hospital controls, report a higher frequency of appendectomies in the control group compared to the present study. One might argue that, in general, hospital controls have earlier access to the hospital than population-controls. Abdominal complaints in such a group might result more frequently in a visit to the hospital. In some of the members of this group this might lead to surgery of the -healthy or inflamed-appendix.

Furthermore, in our study, controls were age- and sex-matched and pairwise analyzed, in contrast to the controls used in three of the former studies^{4,6,7}. The

exposure status (appendectomy or not) was measured according to information gathered by a mailed questionnaire. Recall bias cannot be excluded, but few arguments for a difference in recalling surgery of the appendix seems to be present. Cases and controls were pairwise matched for age and sex, in contrast to the Belgian study in which controls were older than cases, possibly overstating a presumed protective effect⁷. Furthermore, it could not be excluded that many of the appendectomies in controls were performed after the patients' age of disease onset¹³. To be able to recognize a protective or a risk factor, it is evident that the reference procedure has to be performed before diagnosis. This was the reason for us to ignore appendectomy in cases if performed after IBD diagnosis and in controls where it was performed after IBD diagnosis of the paired case.

Confounding by smoking, the only factor consistently associated with UC (negatively) and CD (positively), was ruled out in the present study, but not in all four preceding studies¹⁴⁻¹⁷. We cannot be sure, however, that other confounding factors might explain our results.

To associate a factor with the occurrence of a disease, a biological hypothesis is needed. In UC the equilibrium between T-helper and T-suppressor cells is shifted in favor of the T-helper cells. A suggested biological explanation for appendectomy to protect against development of UC is that removal of the appendix, a T-helper cell organ, might change the balance in favor of T-suppressor cells and thus prevent the inappropriate immune response⁷. However, it remains difficult to perceive why removal of a relatively small quantity of gut-associated lymphoid tissue should have such a profound effect¹³.

In conclusion, this is the first study also investigating the relationship between appendectomy and the risk of IBD in incident patients. Overall, a protective role of appendectomy was found in UC, which reached significance in the prevalent group, whereas a trend towards the same direction was observed in the incident cases with this disease. In CD the trendwise positive association with the operation could almost totally be explained by the number of appendectomies performed close to the time of diagnosis of IBD, suggesting that surgery was due to still undiagnosed CD. The significant association in the subgroup of patients with ileocolic disease is also in favour of this hypothesis.

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Chapter VII

Inflammatory Bowel Disease: Is there any relationship between smoking status and disease presentation? Results of the European collaborative study on Inflammatory Bowel Disease

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Submitted for publication

Abstract

Background: Smoking is associated with Crohn's disease and non-smoking with ulcerative colitis; however, no data have been published on Inflammatory Bowel Disease characteristics at presentation in relation to smoking status.

Objective: To compare clinical features at diagnosis and during the first year of follow-up in smokers and non-smokers amongst newly-diagnosed patients with IBD across Europe.

Design: Prospective study.

Setting: 19 centres across Europe.

Patients: 457 newly-diagnosed patients with Crohn's disease and 930 with ulcerative colitis with complete mapping of disease location.

Measurements: Disease characteristics as well as smoking habits were recorded by the treating physician on a standardized proforma at diagnosis, and treatment characteristics after one year of follow-up. Logistic regression analysis was applied to investigate clinical variables depending on smoking status.

Results: Weight loss occurred significantly more often in smoking patients with Crohn's disease as well as in smokers with ulcerative colitis ($p < 0.02$), and diarrhoea was more frequent in smoking Crohn's disease patients compared to non-smoking ($p < 0.01$). Abdominal pain was reported less often in "ex-smokers" with ulcerative colitis ($p < 0.04$). Smoking patients with Crohn's disease had less frequent colonic involvement ($p < 0.01$), and were more often prescribed immunosuppressive medication ($p < 0.02$).

Conclusion: Smoking seems to protect the colon from inflammation and is associated with a negative disease development in Crohn's disease. The association between weight loss and smoking in both diseases is probably due to a general effect of smoking. The reported relationship between smoking and the course of Crohn's disease is a strong argument for encouraging patients to give up smoking.

Introduction

During the past decade smoking habits have been identified as strong risk factors in Inflammatory Bowel Disease (IBD), cigarette smoking being associated with the development of Crohn's disease (CD) and non-smoking or, perhaps more exactly, stopping smoking with ulcerative colitis (UC)¹⁻¹⁰. Furthermore, in CD smoking is associated with an impaired prognosis and a reduced quality of life¹¹⁻¹⁴. In active UC treatment with nicotine improves disease activity, suggesting a beneficial effect of smoking¹⁵⁻¹⁹. However, no data have been published on differences between smokers and non-smokers at time of diagnosis of IBD.

The aim of the present study was to compare clinical features at diagnosis in smokers and non-smokers in a large inception cohort of newly-diagnosed patients with IBD across Europe. Secondly, as markers of the disease course, the rate of surgical resections and the frequency of immunosuppressive medication use were compared in both groups.

Patients and Methods

Demographic and medical data of the patients included in the EC-IBD study were used in the present analysis. This prospective study, a concerted action of twenty European centers (appendix), investigated primarily the incidence of IBD in the North and South of Europe during the period 1991-1993. Beyond this, the protocol of the study was also designed to study clinical features and putative risk factors for IBD. The methods and results of the main study have recently been reported in detail²⁰.

A uniform proforma was used by all centers and completed for each patient when the diagnosis was first made. One year later a follow-up form was completed giving additional information and any change in diagnosis. Besides medical data at presentation and at the one-year follow-up, findings such as age at diagnosis, gender, disease location, extraintestinal manifestations, smoking behavior, oral contraceptive use, and family history of IBD at diagnosis were recorded. As only a small minority of the patients were pipe or cigar smokers, it was decided to examine cigarette smoking only. This variable was divided into "non-smokers", "current smokers" and "ex-smokers" at time of diagnosis. Since data on smoking behavior were not available from Amiens (North-West France), patient data of this centre were excluded from the present analysis ($n = 123$ of a total of 2201).

Disease definition

IBD was diagnosed, after exclusion of infections and other recognized causes of

inflammation, on the basis of endoscopic and/or radiological evidence, supported -whenever possible- by mucosal biopsy and/or examination of a surgical specimen. The criteria of Lennard-Jones were applied in case definition for CD, taking into account both macroscopic and microscopic features²¹. UC was defined as continuous mucosal inflammation without granulomata, affecting the rectum without or with some or all of the colon in continuity with the rectum. Using all available medical information obtained around the time of diagnosis, location of the disease in the large and small bowel was carefully recorded. CD was subdivided into small bowel disease only, colonic disease only, and combined small and large bowel disease (also including small bowel plus coecal involvement). UC was subdivided into ulcerative proctitis (endoscopic extension distal to the rectosigmoidal junction), left-sided colitis (inflammation up to, but not beyond, the splenic flexure) and pancolitis (inflammation beyond the splenic flexure). CD patients were excluded when no investigation of the small bowel and the colon had been performed, as were UC patients without mapping of the colon beyond the splenic flexure. The definite diagnosis after one year of follow-up was used in the present analysis.

Statistics

Most data are presented as number of patients with percentages in brackets. Age is given as median and range. The variable smoking was divided into "never-smokers", "ex-smokers" and "smokers" at time of diagnosis. Smoking habits between UC and CD were compared using the chi-square test. Logistic regression analysis was used to investigate a possible association between clinical features and smoking. Clinical features studied were: disease location, weight loss, diarrhoea, abdominal pain, extraintestinal diseases, perianal disease at diagnosis, and -as markers of the disease course- immunosuppressive drug use and surgical intervention during the first year after diagnosis. To minimize confounding, the variables oral contraceptive use, positive family history of IBD, age at diagnosis, and gender were also taken into account in the analysis. The continuous variable age at diagnosis was divided into three categories: "below 25", "between 25 and 60", and "above 60 years". Data analysis was performed with the SPSS package 6.0 for Windows and the S-Plus data analysis package. P-values less than 0.05 were considered as statistically significant.

Results

Data were available of 630 incident patients with CD and 1317 incident patients with UC distributed over 19 participating centers. Of the patients with CD

complete mapping of the colon and the small bowel had been performed in 457 (73%) and of those with UC the full colon (beyond the splenic flexure) was examined in 930 (71%) patients. The demographic characteristics of the patients with complete disease mapping are shown in **Table 7.1**.

Table 7.1 Demographic characteristics of the patients

	Crohn's disease	Ulcerative colitis
All patients	457	930
Females number (%)	239 (52)	414 (44)
Age at diagnosis (median and range)	30 (15-84)	39 (15-89)
"Current smokers"	48%*	16%
"Ex-smokers"	11%*	34%
"Never-smokers"	41%*	50%
Family history of IBD	5%	4%
Disease location number (%)	130 (28) colon only	345 (37) proctitis
	123 (27) small bowel only	318 (34) left-sided
	204 (45) combination	267 (29) pancolitis

* Chi-square derived p-values

Differences between Crohn's disease and ulcerative colitis: $p < 0.001$

Smoking behavior in CD and UC

Data on cigarette smoking were available for 98% patients with CD and for 97% patients with UC. Cigarette smoking at time of diagnosis was noted more frequently in CD (48%) than in UC (16%) ($p < 0.001$). On the other hand, the percentage of "ex-smokers" was higher in UC (34%) than in CD (11%) ($p < 0.001$); furthermore, the interval between stopping smoking and diagnosis of IBD was shorter in UC than in CD: 50% and 15% respectively had given up smoking within five years before diagnosis ($p < 0.01$).

Smoking and disease location

As shown in **Table 7.2** significantly more "current smokers" than "non-smokers" or "ex-smokers" with CD had small bowel involvement ($p < 0.001$). Logistic regression analysis showed no effect of oral contraceptive use, a positive family history, age at diagnosis or gender on disease location. No effect modification was observed between these variables and the effect of smoking on disease location. Corrected for smoking status and the other variables, small bowel involvement was

Smoking status and presentation

more often observed in females ($p < 0.016$) and in younger persons ($p < 0.026$). In UC, no association between smoking and disease location in the colon was found. However, pancolitis was observed more often in males ($p < 0.001$) and in the oldest and youngest age category ($p < 0.001$).

Table 7.2 Disease location at presentation according to smoking status

Crohn's disease	Current-smokers nr (%)	Never-smokers nr (%)	Ex-smokers nr (%)
colon only	45 (35)	64 (50)*	18 (14)
small bowel only	67 (55)	38 (31)	14 (11)
combination	103 (47)	80 (40)	18 (9)

Ulcerative colitis	Current-smokers nr (%)	Never-smokers nr (%)	Ex-smokers nr (%)
proctitis	50 (14)	171 (50)	113 (33)
left-sided colitis	50 (16)	151 (47)	107 (34)
pancolitis	50 (19)	128 (48)	85 (32)

Logistic regression derived p-value adjusted for age, gender, family history, and clinical variables
Difference between current smokers and non- or ex-smokers: * $p < 0.001$

Smoking and other clinical features at diagnosis

Clinical characteristics at diagnosis and during the first year of disease are shown in **Table 7.3**. Weight loss was observed significantly more often in "current smokers" both in CD ($p < 0.017$) as well as in UC ($p < 0.001$). Whereas no significant difference depending on smoking status was found in the frequency of diarrhoea in UC, "current-smokers" with CD more often reported frequent stools ($p < 0.004$). Abdominal pain was reported less often in "ex-smokers" with UC ($p < 0.04$).

Smoking and disease course during the first year

Steroids or other immunosuppressives (azathioprine, mercaptopurine, cyclosporin) were prescribed significantly more often in smoking CD patients than in non-smoking ($p < 0.02$). This difference was not found in UC. No difference in the frequency of operation or bowel resection depending on smoking status was found in either disease group.

Table 7.3 Symptoms and clinical findings at diagnosis and variables related to the course of disease during the first year depending on smoking status

	Crohn's disease		ulcerative colitis	
	Smokers % positive	Non-smokers (Ex-smokers) % positive	Smokers % positive	Non-smokers (Ex-smokers) % positive
Weight loss (> 5kg)	31 ¹	18 (13)	22 ²	9 (13)
Diarrhoea (> 5 times per day)	59 ³	45 (51)	60	56 (58)
Abdominal pain	61	53 (62)	28	25 (20 ⁴)
Extraintestinal manifestations	14	15 (14)	6	8 (8)
(Peri) anal disease	14	17 (26)	4	2 (3)
Steroid/immunosuppressive use	66 ⁵	57 (57)	52	56 (54)
Surgical resection	19	17 (22)	3	3 (3)

Logistic regression derived p-values adjusted for age, gender, family history, clinical variables and disease location.

Differences between "current-smokers" and "non-smokers" or "ex-smokers":

¹ p < 0.017; ² p < 0.001; ³ p < 0.004; ⁴ p < 0.04.

Difference between "current-smokers" or "non-smokers" and "ex-smokers":

⁵ p < 0.02.

Discussion

The differential association between smoking and the two subtypes of Inflammatory Bowel Disease is well established¹⁻⁸. We were interested in elucidating whether smoking behavior also influences clinical features of IBD at the time of diagnosis and during the first year of follow-up; evidence of a causal relationship between smoking and IBD would be further strengthened if the habit would influence the extension of inflammation, clinical symptoms and signs at presentation, and the course of disease²².

In the present study smokers with CD had more often small bowel involvement at diagnosis than never-smokers or ex-smokers with this disease. No difference in disease location depending on smoking status was observed in UC. To reduce confounding, factors possibly related to characteristics of disease location and to smoking such as gender, age at presentation, oral contraceptive use, and a positive family history of IBD were controlled for by logistic regression analysis. The role of oral contraceptives is an example of a possible interactive risk factor combined

with smoking in CD, the suggested common mechanism being multifocal gastrointestinal infarction^{23,24}. In our study no interaction between smoking and oral contraceptives was observed.

Age at presentation was taken into account, since it might be related to life-time tobacco use in smokers, and gender because of different smoking habits in males and females. Independent of smoking status both age and gender were found to be associated with disease location in UC: males, and persons above 60 years and younger than 25 years, presented more often with a pancolitis. The reason for this observation is not clear, but it is in line with recent reports on the incidence of UC in Norway and in The Netherlands^{25,26}.

Seven studies have, mostly in a side-track, addressed the topic of disease location in prevalent groups of smokers and non-smokers with CD^{11,12,27-31}. In three studies a positive association between smoking and small bowel involvement was observed, whereas the other four did not find any association. The present study -the first investigating clinical features *at diagnosis of IBD*- supports the concept that non-smoking is preferentially associated with colonic disease, and smoking with small bowel involvement²². The finding of opposite smoking habits in CD and UC raises the possibility that smoking may be associated with distribution of inflammation. Does smoking protect the colonic mucosa from inflammation? Or, elaborating a little further on this concept: are smoking habits an important determinant for differential expression of IBD in genetically similarly predisposed subjects³?

The mechanisms by which smoking may be protective in UC and deleterious for CD remain unknown. Smoking increases colonic mucus production which is reduced in UC and decreases intestinal permeability: mechanisms possibly leading to protection of smoking against (ulcerative) colitis, as both factors could limit the exposure to harmful exogenous agents³²⁻³⁴. Furthermore, cigarette smoking has several known effects on immune and inflammatory functions: for example it decreases the helper/suppressor T-cell ratio and reduces tissue levels of prostaglandin E and leukotriene B₄³⁵⁻⁴⁰. For CD Wakefield et al. have proposed as a pathogenic mechanism multifocal gastrointestinal infarction mediated by a chronic mesenteric vasculitis^{24,41,42}. The pro-coagulant effects of smoking could enforce this mechanism in CD. It can also be hypothesized that the richly blood-supplied small intestine is more susceptible to smoking induced vasospasm and thrombosis than the more inert large bowel.

The fraction of patients with abdominal pain, diarrhoea and weight loss was higher in smoking patients with CD than in "non-smokers" or "ex-smokers". After correcting for the other variables, such as disease location, only diarrhoea and weight loss was reported significantly more often in smokers with CD, suggesting more active disease at diagnosis. Surprisingly the latter observation was also found

in UC. A possible mechanism to explain weight loss in smokers with either disease is enhancement of satiety following meal consumption by smoking, acting via increase of brain serotonin release⁴³⁻⁴⁵. This may lead to reduced food consumption in patients, who are already in a stressed catabolic state because of active (bowel) inflammation. We cannot explain the association between ex-smoking and reduced abdominal pain as was found in the present study.

No difference between both groups was observed concerning the presence of anal problems or extraintestinal disease at diagnosis. A higher rate of perianal disease in smoking patients with CD has inconsistently been reported^{11,12,29}. Since studies finding a higher frequency of (peri)anal disease in smokers all concern prevalent patients, these results are difficult to compare with the incident population described in the present study. Another explanation for not finding a difference could be that the fraction of patients with (peri)anal disease at the time of diagnosis was not large enough.

Disease outcome depending on smoking status, as measured by the variables surgical intervention and use of immunosuppressive medication, was not different in UC. This is in line with the findings of two previous studies on this subject, but not with the protective effect of smoking on colonic resection as reported by Boyko et al.^{28,46,47}. Benoni et al. as well as Holdstock et al. concluded that it was difficult to interpret the effect of current smoking in their studies because of the low number of smoking UC patients^{27,28}. Since the number of patients in the present study, including the number of non-smokers, is much higher than in the former reports, this is probably not an important issue. It has to be remembered, however, that we have so far only studied the course during the first year after diagnosis, which period might be too short to obtain a difference.

Treatment with nicotine patches has shown favourable results in active UC, but there is no case for nicotine in maintenance of remission¹⁵⁻¹⁷. The evidence in favor of smoking (as opposed to nicotine alone) is insufficient to warrant its recommendation to UC patients, given the potentially fatal consequences of smoking on other biological structures³⁹.

Whereas no higher resection rate in CD was observed in smokers, immunosuppressive medication was prescribed significantly more often in smokers than in non-smokers in the present study. The difference was small, but has been reported previously and suggests a worse prognosis in smokers with CD^{1,11-13}. In the report of Cosnes et al smoking CD patients required more steroids and other immunosuppressive drugs, and resection rates were higher in smoking patients who were not using immunosuppressive medication¹². The authors concluded that immunosuppressives neutralized the influence of smoking on surgical rates. In his comment on this article, Cottone remarked that the authors did not account for

disease extension, which could be of importance in predicting surgical recurrence⁴⁸. Furthermore, in the majority of the above-mentioned publications selected populations were studied, possibly causing bias by excluding a group of patients with inactive disease. The statistically different results, as were observed in the present study, still have to prove their clinical relevance. The results of the ongoing follow-up study of the European inception cohort of incident IBD patients will hopefully provide more insight in the topic of long-term disease outcome in both subgroups of IBD.

In summary, the course of disease, as measured by the use of steroids and immunosuppressive medication, was less favourable in smoking CD patients. Besides other harmful effects of cigarette smoking in general, the latter finding is a reason to strongly discourage smoking in patients with CD. In this study there was no evidence that smokers with UC do better. Smoking habits also determine some clinical aspects of IBD at diagnosis, such as weight loss and diarrhoea. In CD smoking affects disease location: non-smoking being associated with colonic disease. The finding of more colonic disease in non-smoking CD patients, and the positive association between non-smoking and UC might be due to a common mechanism of smoking protecting the colon from inflammation.

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Chapter VIII

Validation of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ): A health-related quality of life questionnaire in Inflammatory Bowel Disease

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Abstract

Health-related quality of life assessment can benefit several groups involved with health care. The aim of our study was to assess construct validity, reliability, discriminant ability and sensitivity to change of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific quality of life questionnaire. A group of 120 IBD patients completed the IBDQ and two Visual Analogue Scales concerning general well-being and bowel function twice. Fifty-two patients also completed the Short-Form 36 twice. Disease activity was assessed once. Correlations between the IBDQ scores and the global assessments were reasonably high and the IBDQ was shown to be discriminative. High intraclass correlation coefficients between both measurements of the IBDQ were observed in patients who reported no change in bowel complaints. In contrast, significant differences were found between both moments in patients who reported change. The Dutch IBDQ proved to be valid, discriminative and reliable.

Introduction

Physiologic measures of diseases often correlate poorly with functional capacity and well-being and are therefore of limited interest to patients¹. Health-related quality of life (HRQoL) assessment is important for measuring the impact of chronic disease on a patient's state of general well-being^{1,2}. HRQoL differs from disease measurement in that evaluation includes psychosocial as well as disease-related factors. Since psychosocial determinants are not accessible through laboratory tests, validation rests with the patient³.

Self-administered or interviewer-administered questionnaires can be used to measure cross-sectional differences in quality of life between patients or longitudinal changes in the same patient during a period of time. While generic questionnaires provide a summary of health-related quality of life, disease-specific questionnaires focus on problems associated with unique disease states or patient groups. Both type of instruments need to be valid (measure what they are suppose to measure), reliable (give comparable results if measured repeatedly), have discriminant power (are able to discriminate between patients with various disease severity), and sensitive to change (able to measure change over time)^{1,4}. For Crohn's disease (CD) and ulcerative colitis (UC) there are a few specific instruments available⁵⁻¹¹. The Inflammatory Bowel Disease Questionnaire (IBDQ), developed by Guyatt and Irvine, has been shown to be valid and reliable in a clinical setting^{12,13}.

To use a questionnaire like the IBDQ in respondents with a native language other than English requires translation, back-translation, adaptation, and re-establishing the validity and reliability within the new national context⁴. The aim of our study was to investigate the various aspects of validity of the Dutch translation of the IBDQ.

Methods

Questionnaires

The original IBDQ was developed to measure disease-specific quality of life in clinical trials involving patients with IBD¹². This self-administered questionnaire, regarding the patient's situation of the preceding two weeks, contains 32 questions grouped into four health dimensions: bowel symptoms (10 items), systemic symptoms (5 items), social function (5 items), and emotional function (12 items). Responses are graded on a 7-point Likert scale in which "1" represents a very

severe problem and "7" represents no problem at all.

A sequence of two steps was followed during the translation of the IBDQ. The first step involved the translation into Dutch by a panel of two physicians familiar with inflammatory bowel disease, followed by back-translation of the IBDQ by an official bilingual (English-Dutch) translator. Secondly, the back-translation was compared with the original IBDQ and differences between these two versions were looked upon by the panel, which consisted of a researcher in the field of IBD and two gastroenterologists (CP, RS, MR). Changes were made until agreement was found. This Dutch version of the IBDQ was pre-tested in a small group of patients with IBD and proved to be understandable and easy to complete. Completion of the IBDQ took between 15 and 25 minutes.

In patients with CD, disease activity was assessed by the Harvey Bradshaw Index (HBI)¹⁴. In patients with UC it was determined by an index (UCI) described by Levenstein, including four symptoms: haematochezia or passage of mucus, the presence or absence of watery stools; tenemus; and number of daily bowel movements¹⁵.

Visual analogue scales (VAS) were used to assess the degree of bowel function and the state of general well-being experienced by the patients themselves. The VAS consisted of a vertical line with at both ends a statement, in which the bottom represented the worst and the top of the line the best possible situation. A crossline was added to mark the middle. Scores were calculated as percentages of the scale, 0% indicating the least favourable health state to 100% indicating the most favourable health state.

Health-related quality of life was also assessed by a Dutch translation of the non-disease-specific 36-item Short Form Health Survey (SF-36). Translation was carried out as part of a International Quality-of-Life Assessment Project¹⁶. The SF-36 includes multi-item scales, measuring eight general health concepts: physical functioning; role limitations due to physical health problems; bodily pain; general health perception; vitality; social functioning; role limitations due to emotional problems; and mental health^{17,18}. To make a comparison with the IBDQ dimensional scores possible, the eight SF-36 concepts were converted into four dimensions corresponding to the IBDQ dimensions: bowel symptoms, systemic symptoms, social function and emotional function. In this conversion the concept bodily pain represents bowel symptoms; the two concepts general health perception and vitality represent systemic symptoms; the concepts physical function, role limitations due to physical health problems, and social functioning of the SF-36 were combined to allow a comparison with the social function dimension of the

IBDQ; and, finally, role limitations due to emotional problems and mental health were joined to be compared with the dimension emotional function of the IBDQ.

Patients

One hundred and thirty-six patients who were diagnosed as having CD or UC were invited to participate in the study. The criteria of Lennard-Jones were applied in case definition for CD and those of Truelove and Witts for UC, including only patients with extended colitis (inflammation beyond the rectosigmoidal junction)¹⁹. Patients with an ileostomy were excluded. While the majority of the patients were recruited from the outpatients' clinic, some were hospitalised at the time of initial enrolment (n=13).

Participants were asked to complete the IBDQ twice, at an interval of four to six weeks. In addition, they were asked to mark their degree of bowel function and general well-being on the VAS at both assessments. At the second assessment each patient responded to a so called "transition question" concerning bowel complaints; the patients were asked whether their bowel complaints were better, worse or the same as four weeks before.

A subgroup of 52 patients (CD n=32, UC n=20) of the 136 patients, also completed the Short Form 36 (SF-36) at both moments. In this subgroup, also the HBI for CD or the UCI for UC was assessed by a gastroenterologist at the time of inclusion.

Of the 136 patients who were asked to participate in this study, 6 patients (4.4%) refused to take part, 5 patients (3.7%) were excluded during the study because only the first questionnaire was returned and 5 patients (3.7%) were excluded because of an ileostomy. This resulted in 120 participants, 71 with CD and 49 with UC. Although patients were asked to complete all 32 questions, in some cases one or more items were missing. For that reason, IBDQ dimensional scores were not calculated as sum scores, as in the original description of the IBDQ, but as mean values provided that at most one item per dimension was missing¹².

Demographic characteristics of the study population are shown in **Table 8.1**. The main reason for refusal was old age. Patients who took part in the study received standard medical care during the course of the study.

Table 8.1 Demographic characteristics of the study population

	Crohn's disease	Ulcerative colitis
Total number of patients	71	49
Female patients	41	24
Hospitalised	9	4
Duration of IBD (years)	8.1	5.6
Bowel resection	19	1
Age median (range)	36 (15-73)	43 (16-80)

Statistical analysis

Descriptive statistics

All statistical analyses were performed with SPSS package 6.0 for Windows. Descriptive statistics for the patient groups were provided as mean, median, range and frequencies. To determine whether the value of the questionnaire might differ in patients with CD and with UC, construct validity, reliability, and sensitivity to change were analyzed separately for those two diagnoses. T-tests were two-sided, and p-values less than or equal to 0.05 were considered as statistically significant.

Construct validity

Validity examines whether the instrument measures the phenomenon of interest. One approach is the so-called construct validity, which relates scores to a hypothesis or concept. Ideally it is determined by comparison against a gold standard. If no gold standard is available for health-related quality of life, it is advised to use 'proxy measures' for comparison. In this study the proxy measures included disease activity indices (HBI and UCI) and global assessments (VAS and SF-36). Pearson correlation coefficients were calculated to express the relationships between the above assessments and the four dimensional scores of the IBDQ.

Discriminant ability

The discriminant ability of an instrument is the ability to distinguish between groups of interests. In this study the patients were divided into two groups: patients with no or minor bowel complaints and patients with considerable bowel complaints. The VAS scores concerning bowel function as well as the disease activity indices were used to separate the groups. VAS scores less than 55%, HBI scores higher than 6, and UCI scores higher than 3 were considered 'considerable bowel complaints'. To investigate whether the IBDQ was able to discriminate

between the two groups with no or minor and with considerable bowel complaints, the Mann-Whitney U test was used.

Reliability

The reliability of a measure relates to the degree of agreement between two sets of measurements. Repeated measures ANOVA were carried out to assess mean differences in scores and to calculate intraclass correlation coefficients (ICC) between scores at both moments of measurements. For each dimension ICC shows the proportion of total variability accounted for by the variability among persons²⁰. In other words, ICC assesses not only the strength of correlation, but also whether the slope and intercept vary from those expected with replicate measures. Reliability analysis was only carried out in patients who reported no change following the transition question on bowel complaints completed at the second measurement moment.

Sensitivity to change

Sensitivity to change of a measure refers to the ability to detect any clinically important change over time, even if it seems small²¹. In our study sensitivity to change was estimated by a paired t-test between the results of two moments in patients who were identified as feeling better or worse according to the transition question concerning change of bowel complaints. Changes in scores were computed as second assessment minus first assessment, so that positive changes indicated improvement, whereas negative changes indicated deterioration.

Results

Construct validity

Pearson correlation coefficients were calculated for each diagnosis separately. As illustrated in **Table 8.2**, most of the correlations between the disease activity indices and the IBDQ dimensional scores were moderately high (-0.39 to -0.72). In patients with UC, the IBDQ dimension social function as well as systemic symptoms showed a lower correlation with the indices than in patients with CD.

Correlation coefficients between the VAS concerning general well-being and the IBDQ dimensional scores varied between 0.54 and 0.70. The VAS for bowel function and IBDQ dimensional scores correlated best (0.68-0.71) in patients with CD.

Table 8.2 Construct validity of the IBDQ: correlation coefficients between the four IBDQ dimensional scores and proxy measures of quality of life in IBD: disease activity indices, Visual Analogue Scales (VAS) for general well-being and for bowel function, and the dimensional scores of the Short-Form 36

IBDQ Dimensions	Disease activity index*	VAS general Well-being	VAS bowel function	Short-Form 36
Crohn's disease				
bowel symptoms	-0.61	0.61	0.69	0.78
systemic symptoms	-0.70	0.64	0.68	0.83
social function	-0.49	0.65	0.68	0.90
emotional function	-0.55	0.65	0.71	0.91
Ulcerative colitis				
bowel symptoms	-0.72	0.54	0.54	0.69
systemic symptoms	-0.48	0.70	0.46	0.89
social function	-0.39	0.55	0.40	0.50
emotional function	-0.52	0.58	0.45	0.84

* Harvey Bradshaw Index (HBI) for patients with CD and Levenstein index for patients with UC

Regarding the SF-36, correlation coefficients with the IBDQ dimensional scores were high and similar for both diagnoses. The only exception was observed in the social function dimension in patients with UC, which showed a lower correlation than the other dimensional scores.

Discriminant ability

According to the VAS on bowel function 42 patients were classified as having considerable bowel complaints and 78 patients as having no or minor bowel complaints. The Mann-Whitney U test showed a statistical significant difference between the two groups for all four dimensional scores of the IBDQ. For a subgroup of 52 patients disease activity scores were available. Twenty of these patients were classified as having considerable bowel complaints and 32 as having minor complaints according to the disease activity scores. Again there was a significant difference ($p < 0.001$) for all four dimensional scores of the IBDQ between both groups of patients (Mann-Whitney U test).

Reliability

According to the transition question regarding bowel complaints, 75 patients (CD $n=48$ and UC $n=27$) remained stable during the course of the study. **Table 8.3** illustrates the reliability outcomes for each diagnosis separately. Intraclass correlation coefficients were high for all IBDQ dimensional scores, with a range from 0.75 to 0.93. None of the differences between baseline scores and follow-up scores was statistically significant.

Table 8.3 Reliability of the IBDQ: agreement between two sets of measurements, expressed by the intraclass correlation coefficients (ICC) between the IBDQ dimensional scores in patients who reported no change in bowel complaints at two assessments with an interval of four to six weeks

IBDQ Dimensions	Number of pairs	Baseline mean	Follow-up mean	Difference mean	ICC
Crohn's disease					
bowel symptoms	48	5.52	5.53	0.01	0.93
systemic symptoms	48	5.22	5.15	0.07	0.75
social function	45	5.93	5.94	0.01	0.78
emotional function	46	5.47	5.51	0.04	0.88
Ulcerative colitis					
bowel symptoms	27	5.72	5.78	0.06	0.87
systemic symptoms	27	5.09	5.30	0.21	0.91
social function	23	6.06	6.25	0.19	0.78
emotional function	27	5.46	5.69	0.23	0.91

Sensitivity to change

Response to the transition question at the second assessment resulted in 35 patients reporting improvement in bowel complaints and 10 patients reporting deterioration. The number of patients who deteriorated was too small to allow separate analysis. For this reason, the sign of the difference score in every such patient was reversed. All 45 patients who reported change in bowel complaints were included in the analysis for each diagnosis separately (CD $n=22$ and UC $n=23$). The results of the paired t-tests are shown in **Figures 8.1** and **8.2**. Statistically significant differences between baseline and follow-up in all dimensional scores were found in patients with CD. In patients with UC, only IBDQ bowel symptom scores were significantly different between both assessments.

Figure 8.1 Sensitivity to change of the IBDQ: IBDQ dimensional scores in patients with Crohn's disease who -according to the transition question- reported change in bowel complaints at two assessments with an interval of 4-6 weeks

Figure 8.2 Sensitivity to change of the IBDQ: IBDQ dimensional scores in patients with ulcerative colitis who -according to the transition question- reported change in bowel complaints at two assessments with an interval of 4-6 weeks

Discussion

Health-related quality of life (HRQoL) measurement is becoming an important issue in both clinical trials and surveys concerning IBD^{13,22}. Only two European countries have English as their first language, the language used in most HRQoL

instruments in IBD. For the other countries, to be able to set up or to participate in international clinical trials, it is necessary to either use a validated translation of the instrument or to develop a new instrument.

The first step in developing a translated instrument concerns aspects concerning translation procedures. In the present study we used the method of translation, back-translation followed by assessing the final version by means of the judgement of a panel of physicians familiar with IBD.

Theoretically, translation and back-translation have to be performed by official bilingual translators. In our study, the translation of the original IBDQ was done by two clinicians familiar with IBD, followed by back translation by an official bilingual translator. Another approach is to involve, instead of back-translation, a lay panel to comment on the translated questionnaire with the purpose of commenting on, or changing the translated questionnaire, provided that the original meaning is maintained²³. The suitability of the content for the new country has to be tested in later stages of the adaptation procedure.

In addition to the important aspects concerning translation of an existing HRQoL instrument, validation requires repeating the process of reassessing construct validity, reliability, and sensitivity to change of the new instrument⁴. In the present study the performance of the IBDQ, using a Dutch translation, was investigated in patients with CD and UC, the two disease entities for which the original IBDQ was developed and validated¹². As in the Canadian study patients with an ileostomy were excluded, because certain items of the IBDQ are not applicable to them.

As shown in detail in this study, measurement of the construct validity of the Dutch IBDQ, using four proxy measures, was good for both disorders. A higher correlation between the Dutch IBDQ and the SF-36 (a generic health-status questionnaire) was observed than between the Dutch IBDQ and global instruments of disease activity or disease perception (HBI, UCI, VAS). The bowel and systemic symptoms dimensions correlated better with the HBI and UCI than the dimensions of social and emotional function. It has to be mentioned here, however, that the IBDQ questions concerning social and emotional dimensions almost all refer to impairment as a result of bowel dysfunction. For this reason correlations of social and emotional function could be compared to disease activity scales, only taking somatic function into account.

The IBDQ was able to distinguish between a group of patients with considerable bowel complaints and a group with no or minor complaints. Patients were separated using the patients' disease perception (VAS concerning bowel function) as well as the physicians' view on disease activity (HBI and UCI). In both cases

highly significant differences in IBDQ dimensional scores between the two groups of patients were found.

The Dutch IBDQ was shown to be reliable: patients with CD as well as with UC who reported no change in bowel complaints between two time points had comparable scores in all dimensions at both moments, reflected by high ICC values.

Measurement of the sensitivity to change, in the context of the present study, is arguable and is fraught with problems²⁴. It has been disputed whether patients are able to compare their state of well-being between two moments with a transition question²⁵. Probably the best way to assess the sensitivity to change of an instrument is by performing a randomised clinical trial²⁴. However, before using an instrument in a randomised clinical trial, one needs to know if the new instrument is able to detect small and clinically relevant changes over time. An alternative, therefore, is to examine sensitivity to change against an external criterion such as the view of the patient who reports that a change has occurred²⁶. This was the reason for using a transition question concerning bowel complaints to separate stable patients from those who reported change. The transition question was able to discriminate between the group of unstable patients and those who remained stable, according to the SF-36, as well as the VAS on general well-being, and the VAS on bowel dysfunction (data not shown).

In patients with CD who reported change according to the transition question, all four dimensions of the IBDQ showed significant differences between the two moments. Concerning UC, only the dimension bowel symptoms was significantly different. This might reflect a difference between CD and UC. CD in general is more characterised by systemic complaints than UC, and probably also results in more severe social and emotional impairment. In addition, a few more patients with CD were hospitalised at the time of enrolment, therefore more improvement in these patients would be expected. Finally, patients with UC had higher IBDQ dimensional scores at the first assessment, so the possibility of improving scores at the second assessment was less in this patient group.

In contrast to the original Canadian IBDQ, a postal questionnaire was used in the present study. As a consequence of this approach, some questionnaires with missing items were returned. To be able to include most patients, mean scores were calculated for each dimension in the analysis, providing that at most one question per dimension was not completed. Mainly in the social function dimension more than one item was missing, resulting in a decreased amount of paired measurements, as can be observed in Table 8.3. The analysis showed that mostly

the items concerning daily work and/or sexual habits were missing. In everyday practice, the problem of missing items is well known, and the Dutch IBDQ proved to be valid under the prerequisite mentioned.

Recently de Boer et al. reported their results on validation and cross-cultural adaptation of an into Dutch translated IBDQ²⁷. Their main conclusion was that the IBDQ proved to be a reliable and valid measure of quality of life in inflammatory bowel disease. To be able to compare results with other international studies we used, in contrast to de Boer et al., the seven point Likert scale, as was applied in the original IBDQ. Secondly, we used mean scores for each dimension, allowing patients to miss one question in each dimension. While the former study, using the IBDQ once in all patients, focused on reliability, we approached the patients twice to be able to investigate reproducibility and sensitivity to change. Both studies prove that the IBDQ can be validly used in a different culture, with a different language.

In conclusion, the Dutch IBDQ appeared to be easy to use when studying quality of life in patients with IBD. The instrument was shown to be valid and reliable. As far as can be concluded from our data, sensitivity to change was good in all dimensional scores in CD, and for bowel symptoms in UC. Further assessments of sensitivity to change, sometimes referred to as responsiveness, have to be obtained in clinical trials. This item is addressed at this moment in an ongoing clinical trial in patients with CD in remission (Crohn Remission Trial). The IBDQ can be used in the Dutch-speaking IBD population, and our results suggests that it will be feasible to use translations of the IBDQ in non-English-speaking countries. The present study can serve as a guideline in evaluating translated versions of the original IBDQ (Table 8.4).

Table 8.4 Guideline for translating and validating a questionnaire

Translation / back-translation or lay panel

Construct validity

comparison with proxy measurements (Pearson correlation)

Discriminant ability

comparison of two groups of patients (Mann-Whitney U test for independent samples)

Reliability

two measurements 4-6 weeks apart (intraclass correlation coefficient between two moments in stable patients)

Sensitivity to change

during clinical trial or two measurements 4-6 weeks apart (significant difference between two moments in patients with a change in disease activity)

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Chapter IX

Cigarette smoking and quality of life in patients with Inflammatory Bowel Disease

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Abstract

Objective: Smoking has been reported as influencing disease activity in inflammatory bowel disease. The aim of our study was to elucidate the relationship between smoking and aspects of disease-specific quality of life in inflammatory bowel disease.

Design: Cross-sectional study.

Methods: In 1105 prevalent patients with inflammatory bowel disease, diagnosed according to the criteria of Lennard-Jones and Truelove & Witts, disease-specific quality of life was investigated using the Inflammatory Bowel Disease Questionnaire (IBDQ).

Results: In Crohn's disease, smoking females reported a lower quality of life than non-smoking females (all four dimensions of the IBDQ). Using an explanatory model of relationships between the four dimensions for the analysis, it became evident that smoking is associated with more bowel symptoms in young Crohn's disease females, with more emotional dysfunction in all Crohn's disease females, and with more systemic symptoms in all three diagnostic groups with marked bowel symptoms. Moderately smoking male ulcerative colitis patients reported fewer bowel complaints compared to non-smoking male ulcerative colitis patients.

Conclusion: There is a relationship between smoking and disease specific quality of life in both ulcerative colitis and Crohn's disease. The hypothesis is presented that a part of the observed differences in the studied quality of life dimensions with respect to age, sex and disease group are related to concomitant oral contraceptive use.

Introduction

Although the aetiology of Inflammatory Bowel Diseases (IBD) remains obscure, there is now abundant evidence that cigarette smoking is a risk factor in Crohn's disease (CD) and non-smoking in ulcerative colitis (UC)¹⁻¹². Furthermore, smoking may influence disease activity in IBD. In CD a positive relationship between smoking, symptoms and recurrence has been reported, while in UC therapy with nicotine patches reduces disease activity in the acute stage¹³⁻¹⁶.

Assessment of disease activity is known to be difficult in IBD^{17,18}. Investigating the role of exogenic factors on disease activity or the outcome of medical interventions, it might be of great importance also to take into consideration the patients' evaluation of the quality of life.

The purpose of the study here described was to elucidate the relationship between cigarette smoking and different aspects of disease-specific quality of life in UC and CD. The specific hypothesis under investigation was that, due to bowel and systemic complaints, smokers experience a lower quality of life compared to non-smokers in CD, while the opposite is found in UC.

Methods

Patients

All 1105 patients studied were non-hospitalised at time of the investigation and had varying degrees of disease activity. They are participating in the South Limburg Epidemiological Study on IBD, an ongoing project on epidemiology, pathogenesis, and clinical course of IBD in the south-east of The Netherlands¹⁹. The study area has a population of about 640.000 inhabitants, and medical care to IBD patients is provided mainly by specialists working at six hospitals (one university hospital, two general district hospitals, and three local hospitals). Since October 1991 IBD patients, prevalent as well as incident cases, have been reported by their treating specialist to the IBD study centre. Cases that had been reported during the period from October 1991 through November 1994 formed the basis of the study population. All patients had given informed consent for data collection. Medical data were subsequently collected from the medical records and data on smoking and quality of life were assessed by a postal questionnaire. The criteria of Lennard-Jones were applied in case definition for CD and those of Truelove & Witts for UC²⁰. The group of UC patients was further subdivided into patients with disease limited to the rectum, ulcerative proctitis (UP), and into patients with mucosal inflammation beyond the rectosigmoidal junction, extended ulcerative colitis

performed and Cronbach's alpha for internal consistency was calculated^{24,25}. Given the explanatory model between the four dimensions, causal relations were supposed to be present so that four separate factor analyses had to be performed using principal-axis-factoring as analysing technique. Results are shown in **Table 9.1**: all dimensions were unidimensional, as factor loadings were "high" (>0.4) and "second factors" could be neglected. Reliability coefficients turned out to be sufficiently high, so the additive scale construction in the first part turned out to be legitimate. Subsequently analysis of covariance (Ancova) was used for data analysis. Age was considered as a covariate, 'smoking cigarettes' and the intensity of smoking, gender and diagnosis group were the factors. Following the causal order hypothesized in **Figure 9.1**, for instance in analysing systemic symptoms as a dependent variable, 'bowel symptoms' was used as an extra covariate. Using stepwise backward elimination as a guiding line to test all types of interactions between factors themselves and between factors and covariates, the best fitting model was searched which could reproduce the observed scores most efficiently. A p-value belonging to F-ratios of 0.05 was considered to be statistically significant. All data analysis was made using SPSS-pc programs (Dos /5.0 and Windows /6.0).

Results

1. Actual smoking habits

Current cigarette smoking was reported more frequently in CD (45%) than in e-UC (17%) or UP (10%). Correcting for age (below or above 45 years) and gender this difference between CD on the one side and e-UC and UP on the other was statistically significant in females of any age ($p<0.0001$) and in males above 45 years ($p<0.0001$), but not in males younger than 45 years ($p=0.20$). Male e-UC patients above 45 years, were significantly less often smokers than male UP patients above 45 years ($p<0.0001$). No difference between e-UC and UP was observed in females or male patients under 45 years ($p=0.51$). The average number of cigarettes smoked each day, as reported by the patients in the various groups, is illustrated in **Figure 9.2**.

2. Smoking status and IBDQ

The mean scores, standard deviations and numbers of patients of the four dimensions and the total IBDQ score in e-UC and CD are given in the **Figures 9.3** and **9.4**. Data are given by gender and separately for smoking and non-smoking patients. In e-UC and UP (data not shown) no difference between smokers and non-smokers in the mean scores of the total IBDQ score and of the four dimensions was observed. In CD the mean total IBDQ score as well as the mean scores of the

Table 9.1 Factor-analytic results and results of the reliability analysis for the four dimensions ('factors') within the IBDQ. The items are reproduced as a shortening of the original IBDQ²¹.

Bowel symptoms	Factor loading	Systemic symptoms	Factor loading
Abdominal cramps	0.820	Fatigue and tiredness	0.839
Abdominal pain	0.795	Generally unwell	0.831
Abdominal bloating	0.677	Energy	0.788
Frequency of defecation	0.629	Keeping awake	0.540
Loose bowels	0.568	Getting the desired weight	0.394
Accidental soiling	0.560		
Tenesmus	0.547		
Large amounts of gas	0.519		
Rectal bleeding	0.472		
<i>Eigenvalue</i>	3.59 (39.8%)	<i>Eigenvalue</i>	2.46 (49.2%)
<i>Cronbach's alpha</i>	0.85	<i>Cronbach's alpha</i>	0.81
Emotional function	Factor loading	Social impairment	Factor loading
Feeling depressed	0.817	Cancel an engagement	0.807
Feeling tearful	0.801	Problems with sports activity	0.698
Feeling irritable	0.795	Unable to attend work	0.682
Feeling happy	0.776	Avoid events, washroom	0.674
Feeling frustrated	0.752	Limited sexual activity	0.571
Feeling relaxed	0.736		
Feeling embarrassed	0.712		
Worries, complications	0.709		
Feeling angry	0.667		
Lack of understanding	0.573		
Fear of no washroom	0.499		
Fear of needing surgery	0.497		
<i>Eigenvalue</i>	5.96 (49.6%)	<i>Eigenvalue</i>	2.38 (47.4%)
<i>Cronbach's alpha</i>	0.92	<i>Cronbach's alpha</i>	0.82

Note: High factor loadings mean a high correlation of a variable with the factor; the *Eigenvalues* express the total amount of variance explained by the factor; *Cronbach's alpha* reflects internal consistency of the factor

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four dimensions were significantly lower in smokers. After further subdivision by gender these differences were due to significant differences in females only.

3. Explanatory model

In this second part only the significant findings will be given following data analysis with the explanatory model, in which the four IBDQ dimensions are treated as dependent variables and age, gender, smoking habit, and diagnosis as predictors (ANCOVA).

Figure 9.2 Actual smoking behaviour of the study population

Bowel symptoms

Smoking male e-UC patients had a significantly higher (better) mean score concerning bowel symptoms than non-smoking male e-UC patients ($p < 0.04$). Controlled for the number of cigarettes smoked daily, the significance was true only in patients smoking 1-9 cigarettes/day (6.2% of the patients; $p < 0.006$). In female e-UC patients and in patients with UP (of both genders) no difference was found in bowel symptoms between smokers and non-smokers.

In contrast, smoking female CD patients, but only those under the age of 45 years, had a lower (worse) mean score of bowel symptoms than non-smoking female CD patients in this age group ($p < 0.001$; $n = 238$). Above the age of 44 years no difference was found between smoking and non-smoking female CD patients ($p = 0.896$; $n = 75$).

IBDQ Dimension		Bowel		Systemic		Emotional		Social		Total Score	
		mean (sd)	nr	mean (sd)	nr	mean (sd)	nr	mean (sd)	nr	mean (sd)	nr
Smokers	male	5.94 (1.10)	42	5.30 (1.17)	28	5.70 (1.04)	43	6.19 (1.26)	42	5.75 (1.07)	40
	female	5.29 (1.37)	28	4.75 (1.35)	30	5.20 (1.23)	29	5.96 (1.20)	28	5.40 (1.08)	25
Non Smokers	male	5.53 (1.23)	202	5.28 (1.21)	204	5.60 (1.09)	197	6.07 (1.30)	194	5.68 (0.98)	179
	female	5.46 (1.22)	145	5.04 (1.18)	150	5.55 (1.10)	147	6.05 (1.35)	142	5.58 (0.99)	132

Figure 9.3 Four dimensions and total score of the IBDQ in e-UC according to smoking status (top), supplemented with more detailed data involving gender, standard deviation (sd), and number of patients (nr) at the bottom

IBDQ Dimension		Bowel		Systemic		Emotional		Social		Total Score	
		mean (sd)	nr	mean (sd)	nr	mean (sd)	nr	mean (sd)	nr	mean (sd)	nr
Smokers	male	5.48 (1.07)	79	4.98 (1.27)	80	5.51 (1.05)	77	5.86 (1.13)	78	5.50 (0.96)	72
	female	5.07 (1.13)	159	4.65 (1.27)	161	4.99 (1.21)	159	5.58 (1.52)	150	5.03 (1.17)	144
Non Smokers	male	5.68 (0.92)	126	5.30 (1.03)	127	5.70 (0.94)	120	6.13 (1.07)	120	5.72 (0.84)	110
	female	5.54 (0.97)	154	5.03** (1.13)	156	5.57* (1.00)	151	6.12* (0.99)	148	5.60* (0.88)	137

Figure 9.4 Four dimensions and total score of the IBDQ in Crohn's disease according to smoking status (top), supplemented with more detailed data involving gender, standard deviation (sd), and number of patients (nr) at the bottom

Systemic symptoms

In the "systemic symptoms" dimension smoking males with either e-UC or UP reported a lower (worse) mean score than non-smoking male e-UC ($p < 0.05$) or UP ($p < 0.0008$) patients. If only patients with a relatively low mean bowel symptom score (≤ 5) were included, male smokers in all three diseases had lower (worse) scores regarding systemic symptoms compared to male non-smokers (e-UC: $p < 0.019$; CD: $p < 0.028$; UP: $p < 0.025$). No difference in systemic symptoms was observed between smoking and non-smoking females. Independent of the smoking status, CD females with a low (worse) mean bowel score reported generally more systemic symptoms than females with a high score ($p < 0.006$).

Emotional and social function

Concerning the dimension "emotional function", smoking CD females reported lower mean emotional function scores compared to non-smoking females with CD ($p < 0.001$). Smoking had no relationship to social functioning in either of the three disease groups.

Discussion

In this study we report the relationship between current smoking behaviour and disease-specific quality of life in patients with IBD, as defined by the inflammatory bowel disease questionnaire. In a first -conventional statistical- analysis smoking patients with CD had a lower total quality of life score than non-smokers, consistent with our original hypothesis. This difference was found concerning all four dimensions of the IBDQ, but was only significant in females. The conventional analysis did not confirm our hypothesis in patients with e-UC and UP. To elucidate the relationship between smoking and quality of life in IBD in more detail a relational model between the four dimensions was developed. The main results of this second analysis were that in CD smoking is strongly associated with more bowel symptoms in females under the age of 45, while in e-UC male smokers reported fewer bowel symptoms. Additionally, in all three disease groups, male smokers with marked bowel symptoms reported more systemic symptoms than non-smokers. Finally, female smoking CD patients more frequently reported emotional dysfunction, while no relationship between smoking and social function was observed.

Smoking clearly is an important variable in IBD and is associated with an increased risk of developing CD and a decreased risk of developing e-UC⁹. The important observations of Cottone et al suggest that there is a negative effect of smoking on

disease activity in CD. They showed that after surgery for CD the risks of clinical, endoscopic and surgical recurrence were all increased in smokers compared to non-smokers²⁶. A number of other studies also showed a positive, dose-dependent, association between smoking and disease activity in CD²⁷⁻²⁹. It has been suggested that microvascular inflammation and thrombosis may contribute to the pathogenesis of CD³⁰. Independent risk factors for thrombosis, like smoking and oral contraceptive use, could aggravate microvascular damage and enhance disease activity³¹. In UC smoking possibly has a favourable effect on active disease, which may act via nicotine³². A placebo controlled trial on disease activity in UC using nicotine patches has recently been published. In the acute stage nicotine reduced symptoms and endoscopic inflammation¹⁵. However, as was shown by the same group, nicotine did not diminish the number of exacerbations in quiescent UC³³. As was expected patients with CD in the present study were more frequently active smokers than those with UC. There was an exception, however, in the group of males under the age of 45 years, in whom no significant difference in smoking habits was found between CD and UC.

In IBD, quality of life measurement has become popular during recent years and several instruments have been developed³⁴⁻³⁸. For the present study the IBDQ was used in a survey to measure the patients' -disease-specific- quality of life in a cross-sectional way. Originally, the IBDQ had been developed for repeated use in clinical trials. The original article analyzes four dimensions: bowel and systemic symptoms, and emotional and social function²¹. As was reported earlier by Mitchell, our study showed that those four concepts are not independent factors. By constructing an explanation model one hypothesizes interdependencies between the four different dimensions of the IBDQ. Our model assumes that bowel symptoms influence systemic symptoms and that both bowel symptoms and systemic symptoms have influence on emotional and social function (**Figure 9.1**). Using the predictors diagnosis, smoking behaviour, age, and gender, the four dimensions were analyzed by analysis of covariance. In this way it is possible to assess the empirical relations between the predictors and each of the interdependent dimensions of the IBDQ. One might argue that all relations between the four dimensions are reciprocal, for instance by assuming that besides bowel symptoms influencing emotional function the latter dimension may also affect the former^{39,40}. However, many of the items of the IBDQ measuring emotional function are clearly phrased as specific consequences of the general cause of bowel symptoms. Thus it is not very plausible to argue that the IBDQ dimensions will all be mutually dependent on each other. The patients in the present study, all outpatients, seemed in general to have a relatively high quality of life, which is expressed by high mean scores in the four dimensions of the IBDQ compared to previous studies using this instrument^{21,23}. Most of the observed differences are small, although statistically

significant, and the question remains open whether the differences are of clinical significance. Smoking seems to act differently in patients with high disease activity compared to patients with low disease activity. This was seen in the dimension "systemic symptoms" in CD. Only in patients with moderate or severe bowel symptoms was a difference between smokers and non-smokers found, the former having more systemic symptoms. The observed differences in CD between smokers and non-smokers in the dimensions emotional and social function, where lower mean scores were observed in smokers, could almost fully be explained by the effects of bowel and systemic symptoms on those dimensions. The only significant relationship was found in female CD patients, where smoking was associated with lower scores for emotional function.

It has been reported that females in general report a lower quality of life than men^{41,42}. In our study smoking CD females under the age of 45 reported the worst quality of life in the dimension "bowel symptoms". Oral contraceptive use as a risk factor has been studied in both CD and UC⁴⁵⁻⁴⁸. Results are conflicting, but there is a tendency towards a positive association in both diseases. One might speculate that smoking and oral contraceptive use interact and both influence the outcome of the quality of life scores in the different subgroups (younger versus older and male versus female) of patients. To our knowledge there is no literature available concerning the influence of oral contraceptive use on clinical symptoms in IBD. Since we did not have reliable data on oral contraceptive use at the time of the questionnaire, it was not possible to further examine a possible additive effect.

This study adds a new dimension to quality of life studies in IBD. In addition to using the IBDQ as an instrument in clinical trials, it appeared possible to investigate the effect of a specific risk factor on disease-specific quality of life. The reported negative relationships between smoking and quality of life are strong arguments to encourage patients with IBD to give up smoking. The only exception was formed by bowel symptoms in mildly smoking male UC patients. In spite of this last finding, realising other harmful effects of smoking on health, we feel that also this group should be advised to stop smoking. The important finding that smoking is associated with more bowel symptoms in females with CD under 45 years of age is possibly associated with concurrent contraceptive use. Further studies are necessary to analyze the relationships between smoking and oral contraceptive use, disease activity, and quality of life in IBD. To investigate these relationships and to study the effects of cessation to smoke on quality of life in IBD, a follow-up case-control study involving incident patients is in progress.

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Chapter X

General discussion

General discussion

Introduction

The ultimate purpose of clinical epidemiology is to provide important clues as to the nature of diseases and to recognize preventable risk factors¹. The comparison between diseased and non-diseased populations allows the epidemiologist to determine those features requiring further investigation. Epidemiological studies of Inflammatory Bowel Disease (IBD) were first published in the 1950's and 1960's²⁻⁷. In spite of there being many studies, we still know relatively little about the epidemiology of IBD.

Most data on the clinical manifestation, disease course and outcome of IBD originate from referral centres with special interest in IBD. The bias introduced by studying only the referred cases is obvious.

Incidence of IBD

After a period of progression during the sixties and seventies, the incidence of Crohn's disease (CD) in the Western world seems to have reached a plateau at a level of around 6 per 100.000 inhabitants per year in most industrialised areas. In the same time, the incidence rate for ulcerative colitis (UC) has stabilised in northern Europe and North America. Differences in geographical distribution and, particularly, changes over time within one area may provide insights into possible etiologic factors. Comparing incidence rates between different areas, and to a lesser degree also within areas, can be misleading and several problems have to be faced. Besides the fact that it is important to recognise these problems when studying incidence rates, they also apply to investigations of risk factors and of clinical outcome.

First of all the researcher is confronted with the **problem of diagnosis**. The bowel has only a limited capacity of response to differing etiologic agents, such as microbial and parasitic infections or ischemia. The diagnostic facilities needed to differentiate various forms of the non-specific IBD from specific bowel disorders are not equally distributed over the world and observer variation concerning diagnostic techniques like endoscopy, histology, and barium enemas is considerable¹. Several diagnostic classification criteria are used at present, which may lead to incomparable results^{8,9}. In the studies presented in this thesis the criteria developed by Lennard-Jones have been used because of their practical features and their adequacy to distinguish IBD from non-IBD. A second reason for us to apply the Lennard-Jones criteria was the participation in a large-scale European study, in which these criteria are employed by all centers¹⁰.

Then there is the problem of **case ascertainment**: different case finding methods

have been used. Some studies are population-based and others are mainly or exclusively based on hospitalised patients. Investigators also must be aware of the referral pattern for IBD at the venue of a study, which might cause referral bias leading to underestimation of the incidence rate. Until recently, only few centres have prospectively collected cases, which in fact is a 'conditio sine qua non' for investigating incidence rates. According to Ekbom, it is questionable whether more retrospective studies done in a traditional way, counting heads for short periods in areas without a prior assessment of the incidence, will yield any additional information¹¹.

To be able to compare different studies, the incidence rates should be standardised for age- and sex. A further problem is that of **population size, characterisation and geographic definition of the study area**. Compared to most other gastrointestinal diseases the occurrence of IBD is rare and much larger populations are needed to accumulate adequate numbers of IBD patients. According to Calkins, a rule of thumb for IBD studies is about 250.000 persons for studies lasting several years¹².

During the past five years several prospective studies, using the same disease classification and employing comparable case ascertainment protocols, have been initiated by the EC-IBD study¹³⁻¹⁷. The study on the incidence of IBD in the South Limburg area, as is described in **Chapter III**, prospectively collected cases living in a well-defined geographical and administrative area. In - and out - patients with IBD were reported by specialists working in the area and completeness of the data was estimated in a second study using the computerised diagnostic system of the Registration Network Family Practitioners¹⁸. It appeared that of the selected subgroup known at the RNH, all patients with CD, 80% of the patients with extended ulcerative colitis, but only 25% of the patients with proctitis were known to the IBD registry. This proves the importance of quality control of data.

The incidence rate (per 100.000 inhabitants and year) of IBD in the South Limburg area (6.9 for CD, 10.0 for UC and 1.1 for indeterminate colitis) is high compared to the only available data reported for The Netherlands. In a retrospective study during the period 1978-1981 in the Leiden area, Shivananda and co-workers found incidence rates of 3.9 for CD and 6.6 for UC^{19,20}. As disease definitions in both studies are comparable, the higher rates of our study could either be explained by a more complete case ascertainment due to the prospective approach, or else by a real rise in incidence in the last 15 years. Finally, the difference could simply be due to a higher incidence of IBD in our area compared to Leiden; both study populations might differ in genetic background and / or environmental risk factors. The incidence rate of IBD in South Limburg was also higher than in most of the 19 European centres participating in the European Collaborative Study on IBD during the study period October 1991 - October 1993¹³. Continuation of the assessment of

the frequency of IBD in our study area might prove to be important in studying the pathogenesis of IBD.

Risk factors of IBD

Investigating risk factors in IBD confronts the researcher with almost all the problems that have been mentioned in the previous paragraph. Beyond these, some other factors have to be taken into account. Because of the low incidence of IBD, the preferred research design is the case - control approach. The nature of this design requires patients and controls to recall factors before some previous event (like the moment of first complaints). This introduces the concept of bias, defined by Sackett et al. as any systematic deviation of an observation from the true (clinical) state²¹. Bias distorts reality and influences the validity of a study negatively. The deviation can shift the measure of association, such as the relative risk in cohort studies and the odds ratio in case - control studies, towards zero, and away from zero, and bias can even switch the effect parameter. The concept bias can be divided into three major groups: selection bias, information bias, and confounding²². Since most sources of bias are introduced in the design and execution stage of the research, they can no longer be controlled for in the analysis of the results. In most epidemiological studies in IBD relatively little attention is given to the selection of an adequate control population. The importance of choosing comparable controls, meaning that selection - and information - bias is avoided, will be further discussed in this chapter in the light of the studies described in this thesis.

The pathogenesis of CD and UC probably involves an interaction between genetic and environmental factors. The present thesis focuses on three (groups of) risk factors in the development of IBD: genetic factors, 'modern life' factors (including oral contraceptive use and smoking), and appendectomy.

Familial aggregation of IBD, the role of genetics

In Chapter IV the familial aggregation of IBD in South Limburg, a measure for the role of genetic factors in the pathogenesis of IBD, is described. The first analysis of the patient questionnaire concerning IBD occurring in family members showed that inconsistent answers were provided by the patients. It was therefore decided to disregard these data and to perform a new study in a selected well-defined population, who were all interviewed by their doctor. In case of a positive family history of IBD, family members and their general physicians were approached by the researchers to be able to confirm the diagnosis. IBD was reported and confirmed in 16 (out of 1554) first-degree relatives by 11 (out of 245) patients. Prevalence of IBD was highest for siblings (1.5%) and children (1.3%)

whereas only 0.2% of the parents were affected by IBD. Among relatives of the control subjects, IBD was observed in 0.8% (vs. 4.5 % in IBD patients), resulting in an odds ratio of 5.7 (95% CI: 2.0-16.7).

Compared to other studies on familial aggregation of IBD, our figures on the prevalence of IBD in relatives are lower than most others. Crude rates of up to 40% of family IBD history, as well as frequencies of IBD as high as 2% among siblings have been described, but these reports are largely from referral practices, which raises the issue of selection bias. Referral centers usually deal with more seriously ill subjects who may have more family members affected than less seriously ill. A second concern is whether the reports of relatives with IBD are confirmed by inquiry of the relatives themselves or by reviewing the medical records. It was remarkable that, compared with the patients' opinion, a positive family history could only be confirmed in 57% of the relatives in our study. Reports of positive family histories based on diagnoses confirmed by an objective method have ranged from 1 to 8%²³⁻²⁵. Remarkably, our data on the prevalence of IBD in family members are rather consistent with the large, well-designed, population-based study from Copenhagen²⁶. The only Dutch study on familial incidence of CD by Weterman et al. was published in 1984 and reported a prevalence of 8% in a selected population attending a referral hospital²⁷.

As has been observed, prevalence of IBD was higher in siblings and children compared to parents¹⁶⁻¹⁸. It is likely that many offspring of patients have not reached the age at which symptoms become manifest, and the risk to offspring is therefore probably underestimated by the majority of studies, including ours. Since we had no information on the age of all the 1544 relatives, it was impossible to calculate age- and sex- specific prevalence rates or to develop age-corrected empirical risks of IBD, as was done by Yang et al²⁸.

Other evidence for a genetic component in developing IBD comes from twin studies. In a study from Sweden, there was a high concordance rate for monozygotic twins for CD (58.3%), whereas a concordance for UC could be demonstrated for only 6% of the pairs²⁹. The elegance of that study lies not only in the large number of pairs that could be studied, but also in the adjustment for known environmental risk factors, such as smoking. Smoking was significantly related to risk in the same fashion as has been noted elsewhere but when control for this factor was made, neither the genetic nor the smoking factor were sufficient to account for risk. Thus other etiologic risk variables are strongly implicated. However, it has to be realised that, for CD in particular, the coefficient of heritability calculated from concordance rates in twin pairs is greater than that for insulin-dependent diabetes, asthma, or schizophrenia²⁹.

Recently, progress has also been made in studies on chromosomal markers. Linkage studies, determining whether marker alleles are inherited together with the disease of interest, point to a role for the major histocompatibility complex (MHC) class II genes in UC, but not in CD³⁰. These data provide strong evidence for genetic heterogeneity in IBD. Whereas genes of the MHC are implicated as important inherited determinants of UC, in CD important susceptibility genes are likely to exist outside the HLA region. Hugot et al. described recently how, using microsatellites and affected sib-pair analysis, a susceptibility locus for CD could be mapped to chromosome 16³¹. The near future might bring important breakthroughs on the genetic background of IBD.

Environmental risk factors: 'modern life' as a risk factor?

There is no doubt that in the Western world nutritional habits have changed over the past decades. In the same time the incidence of CD and UC have increased to a great extent^{9,32-35}. Food is a major factor affecting the intestinal environment, and the considerable change in dietary habits may explain why IBD has become common. To assess the impact of dietary compounds on disease outcome, researchers are faced with methodological difficulties because the exposure is most often assessed after the diagnosis of disease and the information, therefore, has to be assembled retrospectively. Differential misclassification, the frequency of errors in reporting the exposure level being dependent on having the disease or not, results in over-estimating or under-estimating of effects²². When investigating nutritional risk factors, it is important to recognize and to rule out this kind of error in the design of a study.

In the literature, consumption of refined sugar before or after diagnosis has repeatedly been implicated as a risk factor in CD, and in a few studies also as a risk factor in UC³⁶⁻⁴¹. The increased consumption of sugar could, however, be a secondary phenomenon⁴². Moreover, smoking is positively associated with sugar consumption and any analytical study should take that into account¹¹. Cornflakes and fast food have been implicated as risk factors, as has exposure to dietary yeast in CD. Antibodies to bakers' yeast have been reported among patients with CD but not with UC or other gastrointestinal disorders⁴³. Margarine has been proposed as a risk factor, mainly because the introduction of margarine to the Western world paralleled the beginning of the increase of CD. However, the variations in the dietary intake of margarine was not responsible for the geographical and temporal patterns of CD in an extensive ecological study by Sonnenberg⁴⁴.

In an effort to elucidate the impact of some specific 'modern life' nutritional factors as risk factors to develop IBD, a case-control study was performed in the South Limburg area. The results of this study are presented in **Chapter V**.

Smoking and oral contraceptives were taken into account in the multivariate analysis, as were age, gender and educational class. The major findings of the study were a greater risk for CD among those with a high consumption of chocolate, chewing gum, and cola drinks, and a decreased risk with a high intake of citrus fruits. Except for chewing gum, the consumption of these food items was in a parallel way associated with the development of UC. The highest odds ratios were observed in small bowel CD, which confirms the findings of Persson et al. concerning the intake of sucrose in this subgroup⁴⁵. The investigated items with high OR all share a high sugar content and possibly reflect the changed consumption pattern preceding the rise in incidence of CD and UC. A decreased use of citrus fruits, as has been reported before, was also found to be a risk factor in developing IBD^{46,47}. In our view it might be possible that a modern life-style, equal to frequent fast-food 'dining' as reported by Persson, rather than the intake of a specific nutrient is related to the increased occurrence of IBD. An ongoing study, restricted to newly-diagnosed IBD patients, pairwise matched to controls, will provide more insight into the relevance of the presented findings.

The higher consumption of sugar, if present at all, seemed not to have caused more frequent dentures or dental prostheses in patients than in controls in the setting of our study. Secondly, the interesting and much debated hypothesis on a positive relation between teeth brushing and CD, as reported by Sullivan, could be investigated⁴⁸. No association was found between the presence of CD concerning the frequency of teeth brushing before the first complaints or after the diagnosis had been made.

A striking finding was a decreased risk of UC in non-smokers who had had a toy pet for a period longer than five years. Based on few exposed subjects, the significance of this result might be explained by a minimal differential misclassification. In trying to explain this finding, it might be hypothesized that smoking is a substitute for having a toy-pet in childhood.

A remarkable finding was the positive association between stopping smoking and Crohn's colitis, supporting the hypothesis that smoking protects the colon from inflammation⁴⁹. The consistently reported issue of smoking as a risk factor in CD and stopping smoking as a risk factor in UC was confirmed in our study. Oral contraceptive use, in some studies regarded as a risk factor in CD and to a lesser extent also in UC, was not significantly associated with the development of IBD. Here has to be remarked that we have analyzed the use of oral contraceptives at any time period, since data on temporal use appeared to be collected inadequately, which might have masked a true association. A potential mechanism for the role of oral contraceptive use and CD could be similar to that proposed for smoking, that is, multifocal gastrointestinal infarction mediated by chronic mesenteric

vasculitis^{50,51}. Literature on the role of oral contraceptive use in the pathogenesis of IBD remains inconsistent at this moment, and both smoking and oral contraceptive use should probably be regarded as promoters and not as initiators of CD¹¹.

Does Appendectomy protect against the development of UC?

It is ten years ago since Gilat et al., in an international study of childhood factors in IBD, noted the rarity of appendectomies in patients with UC compared to their control population⁵². The authors had no explanation for their findings and until 1994 there were no further reports on this peculiar observation. The group of Rutgeerts, apparently unaware of this publication, then confirmed this finding and even suggested that removal of the appendix might be a useful procedure since the relative risk of developing UC with an intact appendix exceeds the protection associated with smoking⁵³. This study gave rise to some other investigations on the subject, all confirming the negative association between appendectomy and UC⁵⁴⁻⁵⁹. The material of the IBD registry South Limburg appeared appropriate to investigate this interesting association, avoiding some of the possible sources of bias which in our view had been present in the studies published so far (**Chapter VI**). Incident and prevalent patients with IBD were studied separately. Whereas a small protective role of appendectomy was found in the prevalent group in UC, only a trend was observed in the incident cases with this disease. Subgroup analysis only found a significant association in patients with a pancolitis. No significant association was found between appendectomy and the development of CD. Subgroup analysis, however, revealed a significant positive association in the prevalent group with combined small and large bowel CD. A substantial number of appendectomies in CD cases were performed relatively close to the date of diagnosis, which could mean that some of these patients were operated on because of bowel complaints related to CD still undiagnosed at that moment. The observation that mainly combined small and large bowel CD (including the ileocecal location) was associated with appendectomy also supports this view.

Another difference between the South Limburg study and the other studies is the choice of controls. Controls were recruited from persons registered at the general practitioners' offices of the Registration Network Family Practices (RNH)¹⁸. The RNH is a reliable dynamic sampling frame of the Dutch general population¹⁸. In this way cases and controls are representative of the same study base (the set of persons in which diseased subjects become cases), a precondition when studying risk factors in a case-control design⁶⁰. The preceding studies, all using hospital controls, report a higher frequency of appendectomies in the control group compared to the South Limburg study. One can argue that, in general, hospital controls have earlier access to the hospital than population-controls. Abdominal complaints in such a group might result more frequently in a visit to the hospital.

In some of the members of this group this might lead to surgery of the -either healthy or inflamed- appendix. Furthermore, in our study, controls were age- and sex-matched and pairwise analyzed, in contrast to the controls used in three of the previous studies^{52,53,61}. The exposure status (appendectomy or not) was measured according to information gathered by a mailed questionnaire. Recall bias cannot be excluded, but few arguments for a difference in recalling surgery of the appendix seem to be present. Cases and controls were pairwise matched for age and sex, in contrast to the Belgian study in which controls were older than cases, possibly overstating a presumed protective effect⁵³. Furthermore, it could not be excluded that many of the appendectomies in controls were performed after the patients' age of disease onset⁵⁴. The different results between the prevalent and incident groups analyzed in the South Limburg study are possibly due to a selection bias.

The basis of the relationship between appendectomy and UC remains unclear. In a recent comment on the subject the group of Rutgeerts suggests that appendectomy may protect against the development of UC. As a biological explanation they offer that the characteristics of the lymphoid tissue system of the appendix could predispose to colonic inflammation and that the removal of the appendix would suppress this activity⁵⁶. In an interesting comment in the section 'controversies in IBD' of the same issue of 'Inflammatory Bowel Disease' Marion et al. reject this interpretation. They speculate that factors that predispose an individual to develop UC lower the risk of suppurative appendicitis, referring to confounding⁵⁷. In summary, there is probably a negative association between appendectomy and UC, but the association is mainly evident for more severe cases with extended disease. The mechanism remains unknown and we need to know more about the role of the appendix in the gut immune system before accepting the hypothesis of a protective effect of appendectomy⁶². There is no proof that appendectomy is a risk factor in CD.

Smoking and disease characteristics

At present, smoking is the only widely accepted environmental risk factor in CD, as is non-smoking or, more precisely, stopping smoking in UC^{41,49,63,75}. Smoking may also influence disease activity in IBD⁷⁶⁻⁸². Seven studies have, mostly in a side-track, addressed the topic of disease location in prevalent groups of smokers and non-smokers with CD^{72,76,78,83-86}. In three studies a positive association between smoking and small bowel involvement was observed, whereas the other four did not find any association. A higher rate of perianal disease in smoking patients with CD has inconsistently been reported^{76,83,85}. Furthermore, in CD smoking is associated with an impaired prognosis^{76,81,83}.

In active UC treatment with nicotine improves disease activity, suggesting a

beneficial effect of smoking^{79,80,87-89}. However, no data have been published on differences in clinical manifestation between smokers and non-smokers at time of diagnosis of IBD. In **Chapter VII** the results from the analyses of data of the European Collaborative Study on IBD are presented regarding clinical features at diagnosis in smokers and non-smokers in a large inception cohort of newly-diagnosed patients with IBD across Europe. We were interested in determining whether smoking behavior also influences clinical features of IBD at the time of diagnosis and during the first year of follow-up; evidence of a causal relationship between smoking and IBD would be further strengthened if the habit would influence the extension of inflammation, clinical symptoms and signs at presentation, and the course of disease⁴⁹.

The course of disease, measured by the use of steroids and other immunosuppressive medication, was less favourable in smoking CD patients. There was no evidence that smokers with UC did better than non-smokers. Smoking habits also determined some clinical aspects of IBD at diagnosis, such as weight loss and diarrhoea. In CD smoking affected disease location: non-smoking was associated with colonic disease. The finding of more colonic disease in non-smoking CD patients, and the positive association between non-smoking and UC might be due to a common mechanism of smoking protecting the colon from inflammation.

The statistically different results, as were observed in the present study, still have to prove their clinical relevance. The results of the ongoing follow-up study of the European inception cohort of incident IBD patients will hopefully provide more insight in the topic of long-term disease outcome in both subgroups of IBD. Although it is not (yet) proven, it is likely that cessation of smoking will lead to lower incidence rates for CD, lower rates of recurrence, and less severe complications⁹⁰.

Health related quality of life in IBD

One of the more interesting aspects of the history of CD and UC is the change in thought from psychological issues as being causative to their being a consequence of the recurrent intestinal (and extraintestinal) symptoms. Unfortunately, outdated stereotypical characterisations of the personalities of patients with IBD are still heard among the lay public and are mentioned by therapists, who are entrusted with counselling these patients⁹¹. As a result of this change of thought, psychological issues have recently been included in the assessment of disease activity.

The number of disease activity indices in IBD is considerable and during the past

decade also several Health-Related Quality of Life (HRQoL) indices have been developed for application in IBD. Physiologic measures of disease often correlate poorly with functional capacity and well-being and are therefore of limited interest to patients⁹². Health-related quality of life (HRQoL) assessment might be important for measuring the impact of chronic disease on a patient's state of general well-being^{92,93}. So far there are only limited data from studies using validated instruments. An example of a disease-specific HRQoL instrument is the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ), which was developed and validated by Guyat et al. at McMaster University in Canada⁹⁴. HRQoL was assessed by Irvine et al. using the IBDQ during a 18-month trial of low-dose cyclosporin in patients with stable CD⁹⁵. The IBDQ total score and four-dimensional subscores (bowel, systemic, social, and emotional) correlated well with the Crohn's Disease Activity Index (CDAI), but gave more consistent scores than the CDAI in stable patients. In 171 patients who deteriorated during the study, the IBDQ significantly decreased, whilst it was remaining stable in 134 patients who did well. A subgroup of patients requiring surgery experienced more impairment of social function than patients who had flare-ups but did not require surgery, suggesting that perhaps non-disease related features such as personality might lead to surgery in some patients⁹⁶.

The choice of a HRQoL instrument usually depends on the interests and needs of the clinician and investigator. An instrument that can differentiate between persons or groups in terms of a better and worse HRQoL is said to be discriminative. For a discriminative instrument reliability (that is the condition when the variability between patients is greater than the variability within a single patient) is most important. For an evaluative measure responsiveness (that is the ability to detect change) is most important⁹⁷. The disease specific HRQoL instruments that are available for IBD are summarised in **Chapter Ic**. In the patient questionnaire of the South Limburg IBD registry we have chosen to include the IBDQ, since this instrument was at that moment, in our view, the best validated instrument. To use a questionnaire like the IBDQ in respondents with a native language other than English requires translation, back-translation, and re-establishing the validity and reliability within the new national context⁹⁸. The results of this procedure concerning the IBDQ translated into Dutch are described in **Chapter VIII**. The instrument was shown to be valid and reliable. As far as can be concluded from our data, sensitivity to change was good in all dimensional scores in CD, and for bowel symptoms in UC. In contrast to the original Canadian IBDQ, a self-administered form was used in our study. As a consequence of this approach, some questionnaires were returned with missing items. To be able to include the majority of patients, mean scores were calculated for each dimension in the analysis, providing that at most one question per dimension was not completed. The analysis

showed that mostly the items concerning daily work and/or sexual habits were missing. In everyday practice, the problem of missing items is well known, and the Dutch IBDQ proved to be valid under the prerequisite mentioned.

Recently de Boer et al. reported their results on validation and cross-cultural adaptation of an IBDQ translated into Dutch⁹⁹. Their main conclusion was that the IBDQ proved to be a reliable and valid measure of quality of life in Inflammatory bowel disease. To be able to compare results with other international studies we used, in contrast to de Boer et al., the seven point Likert scale, as was applied in the original IBDQ. Whereas the former study, using the IBDQ once in all patients, focused on reliability, we approached the patients twice to be able to investigate reproducibility and sensitivity to change. Both studies prove that the IBDQ can be validly used in a different culture, with a different language.

Recently the main outcomes of HRQoL research in IBD were reviewed by Drossman⁹⁷. He concluded that:

- for most ambulatory patients, HRQoL is generally good
- functional impairment is greater in the psychological and social dimensions than in the physical dimensions
- Patients with CD have greater impairment in HRQoL than those with UC
- There is a strong correlation between disease severity and HRQoL impairment
- Disease-related worries and concerns are associated with psychological distress and poor function, so reduction in these concerns through education and counselling may improve HRQoL
- HRQoL measures correlate better with general well-being than with the physician's rating of disease activity
- For UC, colectomy, regardless of surgical repair, is associated with improved HRQoL, reduced worries about disease, and there was no worsening of body image concerns¹⁰⁰⁻¹⁰².

In an interesting retrospective study using the Sickness Impact Scale (SIP) and the Dutch IBDQ in operated patients with CD, A. Kok and P. Soeters have shown that ileocecal resection improved HRQoL (unpublished manuscript). They found a high correlation between both instruments, and it appeared that the IBDQ was easier to use and less time consuming in this patient group than the SIP.

The possible relation between smoking and the course of disease in CD and UC has already been discussed. In **Chapter IX** the results of our study on the relationship between cigarette smoking and different aspects of disease-specific quality of life in UC and CD are described. The specific hypothesis under

investigation was that, due to bowel and systemic complaints, smokers experience a lower quality of life compared to non-smokers in CD, whilst the opposite is found in UC. In general, a negative relationship between smoking and quality of life was found. The only exception was formed by bowel symptoms in moderately smoking male UC patients. The important finding that smoking was most strongly associated with more bowel symptoms in females with CD under 45 years of age, is possibly associated with concurrent contraceptive use. Further studies are necessary to analyse the interrelationships between smoking and oral contraceptive use, disease activity, and quality of life in IBD. The reported negative relationships between smoking and quality of life are once more strong arguments to encourage patients with IBD to give up smoking. However, in the personal experience of the author, although it appears easy to convince patients of the benefits of giving up the habit, it remains difficult to really stop. It might be worthwhile to set up a detoxification program for patients with CD, who probably have even more advantages from non-smoking than the rest of the population.

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Chapter XI

**Summary and
concluding remarks**

Summary and concluding remarks

The present thesis reports the development of a population-based Inflammatory Bowel Disease Registry in South Limburg, The Netherlands. The methods and basic results of this registry until June 1996 are presented in **Chapter II**.

The aims of the studies addressed in this thesis were: 1) to investigate the incidence of Inflammatory Bowel Disease (IBD) in a prospective way and 2) to study genetic and environmental risk factors in IBD; 3) to elucidate the effect of smoking on disease characteristics at presentation and disease development during the first year of follow-up and 4) to validate the Dutch translation of a Health Related Quality of Life Questionnaire (the Inflammatory Bowel Disease Questionnaire) which was subsequently used as a tool to investigate the influence of the risk factor smoking on the course of the disease.

In **Chapter Ia** a critical overview of the present epidemiological knowledge concerning IBD, focussing on incidence and risk factors, is presented. In summary, an increasing high incidence for both Crohn's disease (CD) and ulcerative colitis (UC) in industrialised countries is reported, reaching a plateau phase during the 1960s and 1970s in UC and recently in CD. In developing countries the occurrence of IBD seems to be lower but growing after the implementation of a Western life style.

In developing IBD, genetical influences are of importance. However, epidemiological studies strongly point to possible interactions between genetically determined features and environmental factors. Of these environmental factors smoking is the most consistent, being of negative influence in CD and protective in UC. Diet and oral contraceptives may influence disease expression, and perinatal events -like viral infections- may alter adult susceptibility. Preconditions for epidemiological studies in IBD, in the view of the authors, are outlined. Most important in defining the role of risk factors is the use of a population-based registry and of population-controls. Furthermore, risk factors should be studied in connection with each other, and finally, investigating subgroups of IBD might prove to be worthwhile.

In **Chapter Ib** a review is presented on Health Related Quality of Life (HRQoL) in IBD. HRQoL is a global concept that incorporates the patients' perceptions, attributions, and daily level of functioning in response to an illness. Three main types of instruments including global assessments, generic instruments, and disease-specific instruments are discussed. The evaluation of HRQoL is important for measuring the impact of chronic diseases and can broaden our understanding of the impact of these diseases in a manner that cannot be accomplished through traditional methods.

The thesis outline and aims of the study are summarised in **Chapter 1c**.

In **Chapter III** the incidence of IBD in South Limburg, The Netherlands, is reported using standardised reports of newly-diagnosed patients. During a four year study a mean standardized incidence rates (per 100.000 inhabitants and year) of 6.9 (95% CI: 5.9-7.9) for CD, 10.0 (95% CI: 8.7-11.2) for UC, and 1.1 (95% CI: 0.7-1.5) for indeterminate colitis were calculated. Estimated case ascertainment, using the database of the Registration Network Family Practices as a reference, was 100% for CD, 80% for extended colitis, but only 25% in ulcerative proctitis. The results suggest a high incidence rate of IBD in The South Limburg area, which is higher than previously reported in The Netherlands and higher than published by centers in most surrounding countries.

To investigate the genetics of CD and UC a study on family aggregation of IBD in a subgroup of cases registered at the IBD South Limburg Registry was performed. The results of this study are presented in **Chapter IV**. The observed risk of IBD for first-degree relatives of IBD patients was higher than in controls. However, the risk in our population was lower than has been reported by most other centers investigating this subject, possibly as a result of the population-based character of our study. Furthermore, all diagnoses in first-degree relatives had to be verified according to strict criteria. It was remarkable that, compared to the patients' opinion, a positive family history could only be confirmed in 57% of the relatives. Prevalence of IBD was highest for siblings (1.5%) and children (1.3%) of index patients, whereas only 0.2% of the parents were affected with IBD. Strong disease concordance was found in both groups, and a positive history was somewhat greater among relatives of probands with CD than among relatives of UC.

The results of a case-control study, investigating "modern life" in the epidemiology of IBD with special emphasis on nutritional factors, are presented in **Chapter V**. A total of 688 recently diagnosed patients, 290 with CD and 398 with UC, and 616 population-controls were selected for this study. Smoking, age, gender, and educational level were taken into account by using logistic regression-analysis. As has been consistently reported before, smoking was positively associated with CD, whereas non-smoking and stopping smoking both were associated with UC. No differences were found as far as the use of oral contraceptives was concerned.

A positive association with the consumption of cola drinks, chewing gum, and chocolate, and a negative influence with citrus fruit consumption and the development of CD was found. Consumption of cola drinks and chocolate were both positively associated with the development of UC, whereas, in UC, a negative association with citrus fruits and having a toy pet for a period longer than five years was observed. No associations with the frequency of tooth brushing and

developing IBD was found. It is concluded that all nutritional items mentioned may either be true risk factors, or they might merely be the expression of a modern lifestyle also involving other causative risk factors for the development of IBD which at present are still unknown.

To elucidate the role of appendectomy as a risk factor in IBD, a case-control study, using a pairwise matched design, was performed (**Chapter VI**). The risk of developing UC, in 232 *prevalent UC patients*, was significantly lower after previous appendectomy (OR: 0.36 (95% CI: 0.15-0.80); subgroup analysis found a protective effect only in pancolitis. In 208 patients with CD the odds ratios were not significantly different; however, a positive association was found in ileocolic disease. A significantly larger proportion of appendectomies in CD was performed close to the time of diagnosis, suggesting that appendectomy in some cases was due to still undiagnosed CD. No significant associations were observed in *incident IBD patients*. The fact that sex- and age-matched population-controls were used in our study may contribute to a less pronounced association between appendectomy and UC than recently reported by others.

Smoking is associated with CD and non-smoking with UC; however, so far no data have been published on IBD characteristics at presentation in relation to smoking status. In **Chapter VII** a prospective study is presented concerning clinical features at diagnosis and during the first year of follow-up in smokers and non-smokers amongst newly-diagnosed patients with IBD across Europe. The main findings were that weight loss occurred significantly more often in smoking patients with CD than in smokers with UC, and diarrhoea was more frequent in smoking CD patients compared to non-smoking. The association between weight loss and smoking in both diseases is probably due to a general effect of smoking, acting via increase of brain serotonin release. Smoking CD patients had less frequent colonic involvement. Smoking seems to protect the colon, in both CD and UC, from inflammation. The course of disease, as measured by the use of steroids and other immunosuppressive medication, was less favourable in smoking CD patients, a reason to strongly discourage smoking in patients with CD.

In **Chapter VIII** a study is described which had the aim of assessing the validity of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific quality of life questionnaire. This self-administered questionnaire contains 32 questions grouped into four health dimensions: bowel symptoms, systemic symptoms, social function, and emotional function. The Dutch version of the IBDQ appeared to be easy to use and was shown to be valid, discriminative, and reliable. Sensitivity to change was good in all dimensional scores in CD, and for bowel symptoms in UC. The IBDQ can be used in the Dutch-speaking IBD

population, and the results of this study suggest that it will be feasible to use translations of the IBDQ in non-English-speaking countries.

In **Chapter IX** a study is reported with the aim of elucidating the relationship between smoking and aspects of disease-specific quality of life in IBD. In 1105 patients disease-specific quality of life was investigated using the IBDQ. In CD, female smokers reported a lower quality of life than female non-smokers in all four dimensions of the IBDQ. Using an explanatory model of relationships between the four dimensions for the analysis, it became evident that smoking is associated with more bowel symptoms in young CD females, with more emotional dysfunction in all CD females, and with more systemic symptoms in all three diagnostic groups with marked bowel symptoms. Moderately smoking male UC patients reported fewer bowel complaints compared to non-smoking male UC patients. It is concluded that there is a relationship between smoking and disease-specific quality of life in both UC and CD. The hypothesis is presented that several of the differences observed in the quality of life studied dimensions with respect to age, sex and disease group are related to concomitant oral contraceptive use.

The general conclusion to be drawn from these studies is that a near-complete population-based registry of IBD patients in combination with population-based control groups is suitable for providing answers in widely diverse clinico-pathological questions, including pathogenesis, clinical presentation, symptomatology, co-morbidity, and quality of life. Future studies employing this registry may deal with the impact of therapy and disease course, and the influence of health care mechanism in the long-term development of IBD.

Chapter XII

Samenvatting

Samenvatting

Het proefschrift beschrijft de opzet van een 'Inflammatory Bowel Disease' (chronische inflammatoire darmziekten) registratie in Zuid Limburg. Dit is een registratie waarin gegevens van patiënten met de ziekte van Crohn (CD), aspecifieke colitis (IC) en colitis ulcerosa (UC), woonachtig in Zuid Limburg, worden opgenomen.

De volgende onderwerpen worden in dit proefschrift behandeld:

- 1 het op een prospectieve wijze vaststellen van de incidentie van chronische inflammatoire darmziekten (IBD)
- 2 het bestuderen van genetische en exogene risicofactoren bij IBD
- 3 het verschaffen van meer duidelijkheid over de rol van roken ten aanzien van de kenmerkende eigenschappen van de ziekte op het moment van de diagnose en gedurende het eerste jaar van de follow-up
- 4 het valideren van de Nederlandse vertaling van de Inflammatory Bowel Disease Questionnaire (IBDQ), een gezondheid gerelateerde kwaliteit-van-leven vragenlijst (HRQoL).

Deze vragenlijst werd vervolgens als meetinstrument gebruikt om de invloed van de risicofactor roken op het ziektebeloop van IBD te bestuderen.

Hoofdstuk I is een introductie van de onderwerpen die in het proefschrift worden behandeld.

In **Hoofdstuk Ia** wordt een kritisch overzicht van de huidige epidemiologische kennis van IBD gepresenteerd. Er worden stijgende incidentie cijfers voor zowel de ziekte van Crohn (CD) als voor colitis ulcerosa (UC) gerapporteerd in geïndustrialiseerde landen. Gedurende de jaren zestig en zeventig lijkt er in deze streken voor UC en meer recent ook voor CD een plateau te zijn bereikt. In zich ontwikkelende landen is de incidentie van IBD lager maar stijgende, mogelijk door aanname van een meer Westers georiënteerde levensstijl.

Bij het ontstaan van IBD spelen genetische invloeden een rol. Epidemiologisch onderzoek wijst er echter duidelijk op dat hiernaast ook interacties tussen genetische en omgevingsfactoren van belang zijn. Van deze omgevingsfactoren is roken het meest duidelijk. Roken is positief geassocieerd (risicofactor) met het ontwikkelen van CD en negatief geassocieerd (beschermende factor) met het ontwikkelen van UC. Voedingsfactoren en pilgebruik beïnvloeden mogelijk de ziekte expressie, en perinatale gebeurtenissen - zoals virale infecties - veranderen mogelijk de gevoeligheid voor IBD op volwassen leeftijd. Bij de bestudering van risicofactoren is het gebruik van zogenaamde populatie-controles en populatie-gebaseerde registraties van patiënten het meest belangrijk. Tevens moeten

mogelijke risicofactoren in relatie met elkaar worden bestudeerd, en lijkt het zinvol om subgroepen van IBD patiënten te onderscheiden.

In **Hoofdstuk Ib** wordt een samenvatting gegeven van het onderwerp kwaliteit-van-leven, 'Health Related Quality of Life' (HRQoL). Drie soorten meetinstrumenten (globale belasting, generische instrumenten en ziekte-specifieke instrumenten) worden besproken. De evaluatie van HRQoL kan het begrip voor de invloed van deze ziekten op het dagelijks leven verruimen.

De vraagstellingen en de opzet van het proefschrift worden in **Hoofdstuk Ic** beschreven.

De methodes van de opzet van de Zuid Limburgse IBD registratie en de basale resultaten hiervan worden aan de orde gesteld in **Hoofdstuk II**.

In **Hoofdstuk III** wordt verslag gedaan van het onderzoek naar de incidentie van IBD in Zuid Limburg, waarbij gebruik gemaakt werd van gestandaardiseerde rapportages van nieuw gediagnostiseerde patiënten in de regio. Gedurende een vier jaar durende prospectieve studie werden de volgende gemiddelde incidentie cijfers (per 100.000 inwoners en per jaar) met het bijbehorend 95% betrouwbaarheids-interval berekend: CD: 6.9 (95% CI: 5.9-7.9); UC: 10.0 (95% CI: 8.7-11.2) en indeterminate colitis: 1.1 (95% CI: 0.7-1.5). De compleetheid van de registratie werd geschat aan de hand van onderzoek samen met het Registratienet Huisartspraktijken (RNH). Wanneer het RNH als referentie werd gebruikt bleek 100% van de patiënten met CD, 80% van de patiënten met UC, maar slechts 25% van de patiënten met een chronische proctitis bij de IBD registratie bekend te zijn. De resultaten van deze studie geven aan dat er een hoge incidentie van IBD bestaat in Zuid Limburg, hoger dan in het verleden voor Nederland werd gerapporteerd (Leiden en omgeving), en hoger dan in de meeste ons omringende landen.

Familiair voorkomen van IBD, als maat voor de genetische invloed bij het ontstaan van deze ziekten, in een subgroep van de patiënten van de IBD Registratie wordt beschreven in **Hoofdstuk IV**. Het risico op IBD voor eerste graads familieleden (waaronder hier werd verstaan ouders, kinderen en broers/zussen) van IBD patiënten was groter dan bij controles. Het risico was echter minder groot dan door andere centra is gerapporteerd, mogelijk door het populatie-gebaseerde karakter van de Zuid Limburgse studie. Daarnaast moesten alle IBD diagnoses van de familieleden voldoen aan dezelfde strikte criteria voor ziekteclassificatie als de index patiënten. Het bleek dat een positieve familie anamnese bij slechts 57% van de door de IBD patiënten opgegeven positieve familieleden kon worden bevestigd. De prevalentie was het hoogste voor broers/zussen (1.5%) en kinderen (1.3%), terwijl slechts 0.2% van de ouders IBD bleek te hebben. Er werd een sterke ziekteconcordantie gevonden voor zowel CD als UC, en een positieve familie

anamnese werd iets vaker geobserveerd bij CD dan bij UC.

'Modern life' en de epidemiologie van IBD, met speciale aandacht voor voedingsfactoren, is de titel van **Hoofdstuk V**. Voor deze studie werden 688 recent gediagnostiseerde IBD patiënten, 290 met CD en 398 met UC, en 616 populatie-controles geselecteerd. Voor controle van mogelijk versturende variabelen (roken, leeftijd, geslacht en opleidingsniveau) werd gebruik gemaakt van logistische regressie analyse. Zoals herhaaldelijk beschreven bleek roken positief geassocieerd te zijn met CD en zowel niet roken als het stoppen met roken met UC. Er werd geen verschil gevonden wat betreft het gebruik van de pil.

Er werd een positieve associatie tussen de consumptie van cola, kauwgum, en chocolade, en een negatieve invloed tussen de inname van citrus vruchten en CD gevonden. Consumptie van cola en chocolade waren beiden positief geassocieerd met UC, terwijl er een negatieve associatie werd geobserveerd tussen zowel consumptie van citrusvruchten als het langer dan vijf jaar hebben van een troeteldier en UC. Er werd geen verschil gevonden in de frequentie van tandenpoetsen of in het al dan niet hebben gehad van borstvoeding tussen patiënten en controles. Geconcludeerd werd dat alle bovengenoemde voedingsfactoren daadwerkelijke risicofactoren kunnen zijn, of misschien de uitdrukking zijn van een moderne levensstijl die ook andere oorzakelijke risicofactoren voor het ontwikkelen van IBD bevat.

Om meer duidelijkheid te verkrijgen over de rol van appendectomie als een mogelijke risicofactor voor IBD werd een paarsgewijs gematcht patiënt-controle onderzoek uitgevoerd (**Hoofdstuk VI**). In de **prevalente groep** bleek het risico op het ontstaan van UC significant lager te zijn na een voorafgaande appendectomie (OR: 0.36 (95% CI: 0.15-0.80)). Subgroep analyse liet echter alleen een negatieve associatie zien in de groep patiënten met een pancolitis. Bij de ziekte van Crohn werd geen significante associatie tussen appendectomie en het verkrijgen van de ziekte gevonden, hoewel subgroep analyse hier een positieve associatie tussen appendectomie en ileocecale Crohn liet zien. Een significant groter deel van de blinde darm operaties bij de ziekte van Crohn bleek recent voor het vaststellen van de diagnose te hebben plaatsgevonden. Dit suggereert dat in een aantal gevallen de appendix werd verwijderd in verband met klachten die mogelijk verband hielden met een op dat moment nog niet gediagnostiseerde ziekte van Crohn. Bij de analyse van de **incidente patiënten** werd geen verschil gevonden in appendectomie frequentie ten opzichte van controles. Mogelijk dat het matchen op leeftijd en geslacht van patiënten en controles en de bron van controles een verklaring zijn voor het minder duidelijke effect van appendectomie op een eventuele latere ontwikkeling van UC in onze studie in vergelijking met eerdere studies op dit gebied.

Roken is geassocieerd met het ontstaan van CD en niet roken of het stoppen met roken met het ontstaan van UC. Er zijn echter geen gegevens gepubliceerd over de kenmerkende eigenschappen van IBD op het moment van diagnose in relatie tot het rookgedrag. In **Hoofdstuk VII** wordt een prospectieve studie gepresenteerd die de klinische karakteristieken op het moment van diagnose en gedurende het eerste jaar van de follow-up beschrijft in rokers en niet-rokers met een nieuw gediagnostiseerde IBD in Europa. De belangrijkste bevindingen waren dat gewichtsverlies vaker voorkwam bij patiënten met CD en UC die rookten, en dat diarree vaker werd gezien bij patiënten met CD die rookten in vergelijking met CD patiënten die niet rookten. De associatie tussen gewichtsverlies en roken is waarschijnlijk vooral te wijten aan een algemeen effect van roken, gemedieerd via een verhoging van cerebrale serotonine afgifte. CD patiënten die rookten hadden minder frequent ziekte van het colon en het lijkt erop dat roken het colon beschermt tegen ontsteking, niet alleen in CD maar ook in UC. Het beloop van de ziekte, zoals gemeten middels het gebruik van steroiden en immunosuppressieve medicatie, was ongunstiger bij CD patiënten die rookten. Alweer een duidelijk argument om roken bij patiënten met deze ziekte sterk te ontmoedigen.

Hoofdstuk VIII behandelt de validatie van de Nederlandse vertaling van de Inflammatory Bowel Disease Questionnaire (IBDQ), een ziekte-specifieke kwaliteit-van-leven vragenlijst. Deze vragenlijst bevat 32 vragen, gegroepeerd in vier dimensies: darmklachten, algemene symptomen, emotioneel functioneren en sociaal functioneren. De Nederlandse IBDQ bleek gemakkelijk te zijn in het gebruik en valide. Tevens was de Nederlandse IBDQ discriminatief en bij gelijkblijvende ziekteactiviteit stabiel. De gevoeligheid voor verandering van ziekteactiviteit was goed voor alle dimensies bij CD en voor de dimensie darmklachten bij UC. De IBDQ kan gebruikt worden in een Nederlands sprekende IBD populatie, en de resultaten van onze studie suggereren dat het goed mogelijk is vertalingen van de IBDQ te valideren in andere niet-Engels sprekende landen.

In **Hoofdstuk IX** wordt een studie beschreven met als doel de relatie tussen roken en ziekte-specifieke aspecten van kwaliteit-van-leven in IBD te verhelderen. Kwaliteit-van-leven werd bij 1105 IBD patiënten onderzocht met behulp van de IBDQ. Het bleek dat vrouwelijke patiënten met CD die rookten een lagere kwaliteit-van-leven rapporteerden dan vrouwen met CD die niet rookten (voor alle vier de dimensies van de IBDQ). Wanneer de onderlinge relaties tussen de verschillende dimensies van kwaliteit-van-leven in ogenschouw werden genomen bleek dat roken geassocieerd was met meer darmklachten bij jonge vrouwen met CD, en met meer systemische symptomen bij alle IBD patiënten die ziekteactiviteit aangaven. Mannelijke UC patiënten, die matig rookten, rapporteerden minder darmklachten dan mannelijke UC patiënten die niet rookten. De conclusie van deze

studie was dat er een relatie bestaat tussen roken en ziekte specifieke kwaliteit-van-leven in zowel UC als CD. De hypothese wordt vervolgens nader uitgewerkt dat een deel van de geobserveerde verschillen, in relatie tot leeftijd, geslacht en ziektecategorie, in de bestudeerde kwaliteit-van-leven dimensies gerelateerd zouden kunnen zijn aan het gelijktijdig gebruik van de pil.

De algemene conclusie van de in dit proefschrift beschreven studies is dat een populatie-gebaseerde IBD Registratie in combinatie met populatie-controles geschikt is om antwoorden te verschaffen op sterk uiteenlopende klinisch-pathologische vragen. Deze omvatten ondermeer vragen betreffende pathogenese, klinische presentatie, symptomatologie en kwaliteit-van-leven. Verdere studies, gebruik makend van deze registratie, kunnen mogelijk onderwerpen behandelen als de invloed van therapie en de invloed van kwaliteit van gezondheidszorg op het ziektebeloop bij IBD.

Dankwoord

Dankwoord

Het verrichten van regionaal klinisch-epidemiologisch onderzoek houdt uiteraard samenwerking met vele personen en instanties in. Het is praktisch gezien niet goed mogelijk om iedereen die bij mijn proefschrift betrokken is geweest bij name te noemen, vandaar dan ook: *allemaal hartelijk bedankt voor jullie samenwerking, de lering en het plezier dat er was.*

Enkele uitzonderingen wil ik maken. Allereerst mijn ouders, die mij de mogelijkheid hebben gegeven om in de positie te komen een dergelijk onderzoek te kunnen opstarten. Ik ben jullie beiden, ondermeer hiervoor, zeer dankbaar. Jullie hebben altijd veel belangstelling voor het onderzoek getoond en ik denk dat het manuscript van dit proefschrift het meest nauwkeurig door papa is gelezen (en gecorrigeerd).

Hooggeleerde Stockbrügger, beste Reinhold, de oprichting van een Zuid Limburgse IBD Registratie was jouw idee, waarvoor je mij snel enthousiast hebt weten te maken. Jij bent de drijvende kracht achter dit proefschrift, en naast een duidelijke sturing heb je mij ook steeds de ruimte gegeven voor ontplooiing van persoonlijke initiatieven. Het is voor mij een grote eer om door jou te zijn opgeleid tot gastroenteroloog en om jou als promotor te hebben.

Zeergeleerde Brummer, beste Robert-Jan, vanaf mijn eerste bezoek aan Reinhold was je erbij. Tijdens het onderzoek heb je me bijgestaan met raad en daad, waarvoor mijn hartelijke dank. Zeergeleerde Limonard, beste Charles, het MEMIC is cruciaal geweest bij de opzet en de voortgang van het onderzoek en het ziet ernaar uit dat deze rol in de toekomst voor de Zuid Limburgse en Europese IBD registratie alleen maar belangrijker zal gaan worden. De efficiënte en plezierige samenwerking met jou en alle medewerkers van het MEMIC, waarbij ik met name Jan Bergers, Ruud Schmeitz, Eric van Wijlick, Gregor Franssen, Jacqueline Khalifa, Anneke Partowihono, Gertie Wijnands en Marlène Kruijen wil noemen, wordt door mij zeer gewaardeerd.

Prof Dr HFP Hillen, hoofd Vakgroep Interne Geneeskunde, bedank ik hartelijk voor zijn inzet voor de IBD Registratie Zuid Limburg.

De leden van de beoordelingscommissie, Prof dr JW Arends, Prof Dr PB Soeters, Prof Dr JA Knotnerus, Dr RW Logan en Prof Dr JBMJ Jansen bedank ik voor hun bereidwilligheid het manuscript te lezen en voor het geven van waardevolle adviezen.

Patiënt-controle onderzoek is onmogelijk zonder de medewerking van zowel patiënten als controles (sic!). Vanaf het moment van opzet van de IBD Registratie is de patiëntenvereniging Crohn en colitis ulcerosa Zuid Limburg actief betrokken geweest bij het onderzoek. De ideeën die mensen uit de vereniging en Ilse van Engelshoven in 1991 hebben aangedragen blijken wetenschappelijk gezien in 1997 veel waard te zijn: er zijn nu gegevens van meer dan 1600 patiënten over quality of life en quality of care verzameld. De verdere uitwerking hiervan zal ongetwijfeld een proefschrift kunnen vullen. Het feit dat meer dan 90% van de benaderde patiënten een zeer uitgebreide enquête heeft geretourneerd, geeft de belangstelling en medewerking van de patiënten weer. De controles in ons onderzoek wijken voordelig af van die van de meeste centra in die zin dat het echt populatie-gebaseerde controles zijn. Dit was mogelijk door samenwerking met het

Registratienet Huisartspraktijken (RNH). Naast de huisartsen van het RNH in COROP 39 (Zuid Limburg), hebben met name Jean Muris en Job Metsemakers hierin veel energie gestoken.

De rol van research assistent heb ik, na vele uurtjes achter de computer tijdens de nachtdienst, af kunnen staan aan een zeer professioneel team van Research Assistentes. Dit is denk ik een veelzijdige baan waarbij momenten van congres-organisatrice, dia- en poster- ontwerpster, begeleidster van medische studenten en data-entry, afgewisseld worden met de rol van onderzoekster, studiecoördinatrice en analiste. Achtereenvolgens is deze functie ingevuld door Ilse van Engelshoven, Wilke Ellenbroek, en momenteel door Martine van de Kruijs en Ingrid van der Eijk. Allen hartelijk bedankt voor jullie enthousiasme, veelzijdigheid, het steeds weer terugvinden van mijn paperassen en de gezelligheid. Zonder de hulp van vele studentes en studenten bij allerlei aspecten van IBD Zuid Limburg had dit proefschrift niet geschreven kunnen worden. Met name Ingrid Lousberg en Karin Janssen wil ik hier noemen. Ik ben ervan overtuigd dat bij de meeste van hen meer begrip voor chronische darmziekten, een zekere kennis van de ziekte IBD en van onderzoek in het algemeen is ontstaan.

Financiering van een project waarvan nog geen resultaten voorhanden zijn is moeizaam. Ik ben dan ook zeer erkentelijk voor de financiële steun van diverse farmaceutische bedrijven (Astra, Byk, Glaxo, Pharmacia, Tramedico, Yamamouchi), van de Universiteit Maastricht en zeker ook van het Development Fund van het academisch ziekenhuis Maastricht, bij wie ik de afgelopen twee jaar aangesteld was als wetenschappelijk onderzoeker.

IBD Zuid Limburg is destijds ondermeer opgestart om een verdere samenwerking tot stand te laten komen op het gebied van IBD en van de gastroenterologie in zijn algemeenheid binnen de regio Zuid Limburg. Dit is mijns inziens succesvol gebleken en ik ben zeer blij met de goede samenwerking tijdens dit project met vele collega's binnen de regio. Ik hoop dat deze samenwerking zich in de toekomst nog verder zal ontwikkelen. Alle aanmelders van patiënten bij deze hartelijk bedankt. Het is mijn vaste overtuiging dat door klinisch-epidemiologisch onderzoek ook de kwaliteit van zorg en hierdoor ook de kwaliteit van leven bij patiënten met IBD in Zuid Limburg zal verbeteren.

Binnen de vakgroep epidemiologie van de Universiteit Maastricht ben ik vooral veel dank verschuldigd aan Elisabeth Dorant, wiens heldere visie en kritische geest steeds weer resulteerde in een verbeterde versie van het manuscript. Voor de hulp bij de vele, voor mij altijd weer ingewikkelde, statistische bewerkingen wil ik vooral Jan Bergers, Fred Nieman, Jos Thijsen, John Mullink en Alexander Volovics hartelijk danken.

Binnen de werkgroep gastroenterologie van ons ziekenhuis heb ik tijdens de periode van het onderzoek met veel plezier gewerkt. Dame en heren, bedankt voor jullie adviezen, medewerking en prettige werksfeer. Met name de samenwerking met Bertine Geerling, Claudia Pastoor, René Wouters, Ton Vrij en bovenal met mijn huidige kamergenoot en paranymf Eric Schoon is altijd zeer stimulerend en plezierig geweest. We zouden alleen eens wat vaker moeten fietsen! Ik ben ervan overtuigd dat jullie dissertatie, en ook die van Martine van de Kruijs en Ingrid van der Eijk, nog meer gestalte zullen geven aan IBD Zuid Limburg.

Gaby Scheepers, onze werkgroepsecretaresse, was altijd zeer behulpzaam en wist veel

"storingen" te voorkomen, waardoor ik de gelegenheid kreeg om aan dit proefschrift te werken. Tiny Wouters heeft de hoofdrol gespeeld in de laatste fase van dit proefschrift. Niet alleen het op tijd 'drukbaar' krijgen van het manuscript, ook alles er omheen en de manier waarop, hebben voor mij deze laatste maanden zeer plezierig en ontspannen gemaakt.

Lieve Liesbeth, we hadden er voor de aanvang van dit project al één, en gedurende de periode waarin het onderzoek zich heeft afgespeeld is ons gezin nog een stukje groter geworden. Je gezelligheid, je zonnige karakter, je 'management of care and of good quality of life' in ons gezin zijn voor mij steeds het belangrijkste geweest gedurende de afgelopen zes jaar. Lieve schatten, beste kerel, het grote boek is af, kinderhouse mag weer op vol volume!

Curriculum Vitae

Curriculum Vitae

Maurice GVM Russel

1958	Geboren te 's Gravenhage
1976	Eindexamen Gymnasium B
Bisschoppelijk College Roermond
1976	Uitzending Verenigde Staten (AFS)
1977	Studie Geneeskunde
Rijks Universitair Centrum Antwerpen
1978 - 1986	Studie Geneeskunde
Universiteit van Amsterdam
1986 - 1987	Arts-assistent interne geneeskunde
Academisch Medisch Centrum, Amsterdam
1987	Arts-assistent interne geneeskunde
Catharina Ziekenhuis, Eindhoven
1987 - 1992	Opleiding interne geneeskunde
De Wever Ziekenhuis, Heerlen
Opleider: Dr FATH Lustermans
1992 - 1993	Vervolgopleiding interne geneeskunde
Academisch Ziekenhuis Maastricht
Opleider: Prof dr JA Flendrig†
1993 - 1996	Opleiding gastroenteroloog
Academisch Ziekenhuis Maastricht
Opleider: Prof dr RW Stockbrügger
1996 -	Werkzaam als gastroenteroloog
Academisch Ziekenhuis Maastricht
Hoofd: Prof dr RW Stockbrügger

Appendix 1

**EPIDEMIOLOGISCH ONDERZOEK
INFLAMMATOIRE DARMZIEKTEN
IN DE REGIO ZUID-LIMBURG**

EC - IBD

AANMELDING

(door specialist)

na aanmelding,
patiënten dossier
markeren met sticker

Algemene instructies:

- Bij dit onderzoek zijn van belang de patiënten met als diagnose waarschijnlijke dan wel zekere chronisch inflammatoire darmziekten.
- Tot deze ziekten worden gerekend: Colitis Ulcerosa, Chronische Proctitis, ziekte van Crohn en Aspecifieke Colitis.
- Er wordt een onderscheid gemaakt in:
 - nieuwe patiënten: indien één van deze diagnoses in de periode van 1 oktober 1991 tot 1 oktober 1995 gesteld wordt;
 - bekende patiënten: indien één van deze diagnoses reeds vóór 1 oktober 1991 gesteld werd.

Door u aan te melden patiënten:

- Patiënten dienen woonachtig te zijn in de regio Zuid-Limburg, beneden de gemeente Echt.
- Tijdelijke inwoners, zoals militairen, seizoenswerkers en toeristen worden uitgesloten, studenten worden ingesloten.
- Alle nieuwe patiënten (aanmelden a.u.b. op korte termijn na het stellen van de diagnose).
- Zoveel mogelijk bekende patiënten die momenteel bij u onder controle staan.

Ingevulde formulieren:

De ingevulde aanmeldingsformulieren a.u.b. bewaren op de poli, waar ze regelmatig zullen worden afgehaald.

P-AS-VI.1

AANMELDINGSFORMULIER

IDENTIFIKATIE GEDEELTE

(invullen door poli-assistent)

AS-VI.5-a

Naam:

Voornamen:

Adres:

Postcode: [][][][][] Woonplaats:

Geslacht: Geboortedatum: [][][][][][] ddmjj

Naam huisarts:

Naam specialist:

Specialisme:

Ziekenhuis: 1 ☐ Maastricht 4 ☐ Brunssum
2 ☐ Heerlen 5 ☐ Kerkrade
3 ☐ Sittard 6 ☐ Geleen

KODERINGSGEDEELTE

(invullen door roloxdmedewerker)

Registrernummer: [][][][]

Registrernummer: [][][][]

Toestemming: ☐ nee
☐ ja

Invuldatum formulier: [][][][][][] ddmjj

MEDISCH GEDEELTE

(invullen door specialist)

1. a. Wat is de eerste bij deze patiënt gestelde 'IBD-diagnose'?

- 1 ☐ zeker Colitis Ulcerosa 4 ☐ zeker Morbus Crohn
2 ☐ waarsch. Colitis Ulcerosa 5 ☐ waarsch. Morbus Crohn
3 ☐ Chronische Proctitis 6 ☐ Aspecifieke Colitis

b. Op welke datum werd deze diagnose gesteld: [][][][][] mmjj

2. a. Datum eerste konsult: [][][][][] mmjj

b. Duur van symptomen vóór eerste konsult: [][] mm

3. Is patiënt nog bij ander relevant specialisme in behandeling?

☐ nee ☐ ja, zoja:

specialisme	ziekenhuis	gemeente
.....		
.....		
.....		

4. Is de patiënt ooit geopereerd aan de tractus digestivus?

☐ nee ☐ ja, zoja:

jaar	ziekenhuis	gemeente
[1][9][][]		
[1][9][][]		
[1][9][][]		

Specialist: [][][]

Specialisme: [][][]

Ziekenhuis: [][][]

Woonplaats: [][][] CBS kode

Geslacht: [][]

Geb.datum: [][][][][][] ddmjj

Huisarts: [][][]

specialisme	ziekenhuis	gemeente
[][][]	[][][]	[][][]
[][][]	[][][]	[][][]
[][][]	[][][]	[][][]

ziekenhuis	gemeente
[][][]	[][][]
[][][]	[][][]
[][][]	[][][]

AS-VI.5-b

TOESTEMMING VAN PATIËNT

Ik heb er geen bezwaar tegen dat gegevens uit mijn medisch dossier en aanvullende gegevens middels aan mij gerichte enquetes, losgekoppeld van mijn persoonsgegevens, worden gebruikt voor benedenbeschreven onderzoek. Ik weet dat ik ten alle tijde mijn medewerking kan staken en dat, indien ik dit aangeef, ook de bestaande gegevens betreffende mijn persoon uit de registratie zullen worden verwijderd.

Datum:

Naam:

Handtekening:

INFORMATIE VOOR PATIËNT

In 1991 gaat in Zuid-Limburg een onderzoek van start met als onderwerp chronische (=langdurige) darmziekten, waartoe onder andere de ziekte van Crohn en Colitis Ulcerosa behoren. Het doel van het onderzoek is enerzijds zo exakt mogelijk het vóórkomen van deze ziekten en de kenmerken hiervan in Zuid-Limburg in kaart te brengen. Anderzijds is het de opzet door vervolgen van patiënten met langdurige darmziekten een beter inzicht in het beloop van deze ziekten te krijgen. Met deze informatie hopen wij meer medische kennis te vergaren, die gebruikt kan worden om inzicht te krijgen in de oorzaak, het verloop en de behandeling.

Praktisch gezien komt het erop neer dat wij van alle patiënten met een chronische darmziekte een aantal medische gegevens willen verzamelen uit de bestaande medische dossiers. Deze worden aangevuld met gegevens die aan de patiënt, via een schriftelijke enquete, worden gevraagd. Deze gegevens worden vervolgens losgekoppeld van de naam van de patiënt, zodat ze op anonieme basis vergeleken kunnen worden.

Om dit onderzoek waardevol te laten zijn is het belangrijk dat veel, liefst alle, patiënten die in aanmerking komen met het onderzoek meedoen. Derhalve vragen wij uw toestemming om op anonieme basis gegevens uit uw medisch dossier te registreren. Met nadruk wijzen wij erop dat er met deze gegevens uiterst vertrouwelijk zal worden omgegaan en dat zij alleen gebruikt zullen worden om de medische kennis omtrent oorzaak, verloop en behandeling te vergroten. Tevens vragen wij toestemming om middels een aan u gerichte enquete aanvullende gegevens te verkrijgen en via vervolg-enquetes in de loop der jaren de gegevens up to date te houden.

Met dank voor uw medewerking, namens de werkgroep inflammatoire darmziekten Zuid-Limburg,

Prof. Dr. R.W. Stockbrügger
Gastroenteroloog
Academisch Ziekenhuis Maastricht

M.G.V.M. Russel
Internist in opleiding
De Wever Ziekenhuis /
Academisch Ziekenhuis Maastricht

**KRITERIA VOOR DE DEFINITIE VAN IBD* BEHOREND BIJ
EPIDEMIOLOGISCH ONDERZOEK INFLAMMATOIRE DARMZIEKTEN
IN DE REGIO ZUID-LIMBURG**

* Lennard-Jones JE.

Classification of Inflammatory Bowel Disease.

Scand J Gastroenterol 1989, 24(suppl 170):2-6.

Kriteria voor Colitis Ulcerosa:

uitsluiten:

- infectieuze colitis
- ischemische colitis
- bestralings colitis
- solitair ulcus
- afwijkingen suggestief voor de ziekte van Crohn, zoals dunne darm aantasting
- complexe anale laesies
- granulomata

zeker: kontinu mucosale ontsteking zonder granulomata, én rectum aantasting (endoscopie) met een gedeelte van het gehele colon in continuïteit met het rectum (endoscopie of röntgenonderzoek)

waarschijnlijk: symptomen wijzen op Colitis Ulcerosa, maar de criteria zoals bij 'zeker' genoemd zijn (nog) niet aanwezig, omdat het onderzoek nog niet mogelijk of nog niet geheel afgerond is, of omdat de resultaten van het onderzoek (nog) niet goed interpreteerbaar zijn.

Kriteria voor Chronische Proctitis:

Als voor Colitis Ulcerosa, echter alleen aantasting van het rectum (ongeveer eerste 15 cm vanaf anus).

Kriteria voor ziekte van Crohn:

	endoscopie / klinisch	röntgen	biopsi	weefsel
a) Mond tot anus: maagdarmkanaal	+	+	+	+
anus	+		+	+
b) Diskontinu	+	+	+	+
c) Transmuraal: fissuur		+		+
abces	+	+		+
fistel	+	+		+
d) Fibrose: stenose	+	+		+
e) Lymfoid: ulcus			+	+
aggregaat			+	+
f) Slijmretentie			+	+
g) Granuloom			⊕	⊕
Ada mond tot anus: - chronische granulomateuze laesies van lip of wangslimvlies - pyloro-duodenale ziekte (röntgen, endoscopie, biopsi) - dunne darm ziekte (röntgen, endoscopie, weefselonderzoek) - chronisch anale laesie (klinisch onderzoek, biopsi)				
b) diskontinu: - laesies gescheiden van elkaar door normale mucosa, "skip"-laesies of discrete ulcera (röntgen, weefselonderzoek)				
c) transmuraal: - fissuur vormende ulcera (röntgen, weefselonderzoek) - abces (klinisch, beeldvormend onderzoek) - fistel (klinisch, röntgen, weefselonderzoek)				
d) fibrose: - strictuur, eventueel multiple en asymmetrisch (röntgen, endoscopie, weefselonderzoek)				
e) lymfoid: - biopsi waarin klein aphteus ulcus of lymfoïde aggregaten				
f) slijmretentie: - retentie van colon-slijm in biopsi in nabijheid van actieve ontsteking (biopsi, weefselonderzoek)				
g) granuloom: - niet verkazend, niet door vreemd lichaam				

uitsluiten:

- infectieuze colitis (mikrobiologie, eventueel antilichamen tegen Yersinia)
- ischemische colitis
- bestralings colitis
- lymfoom / carcinoom

zeker: volgens bovenstaand schema minstens +++ , of minstens + ⊕

waarschijnlijk: symptomen wijzen op ziekte van Crohn, maar aan de criteria zoals bij 'zeker' genoemd wordt (nog) niet voldaan, omdat het onderzoek nog niet mogelijk of nog niet geheel afgerond is, omdat de resultaten van het onderzoek (nog) niet goed interpreteerbaar zijn of omdat te laag gescoord wordt.

Kriteria voor Aspecifieke Colitis:

Uitsluitcriteria voor Colitis Ulcerosa en ziekte van Crohn niet aanwezig.

Ondanks adequaat onderzoek (momenteel) geen keuze te maken tussen Colitis Ulcerosa en de ziekte van Crohn.

Appendix 2

PATIENT ENQUETE

(invullen indien gegevens niet juist zijn vermeld)

P-V1.9-a

Name: _____

Voornamen: _____

Adres:

Postcode: | | | | | Woonplaats: | | | | |

Geslacht: Geboortedatum: | | || | || 19 | | |

Huisarts:

wel invullen door patient

Gaarne aankruisen dan wel invullen wat op u van toepassing is.

Bijvoorbeeld:

U bent geboren op 12 maart in 1962: 1 1 1 2 1 1 0 1 3 1 1 1 1 9 1 6 1 2 1

U bent geboren in Nederland: ☒ Nederland

ALGEMEEN
(invullen door patient)

(invullen door patient)

Inyuldatum 1 1 11 1 11 19 1 1

1. In welk land bent u geboren?

☐ Nederland Wanneer u niet zeker weet of u de juiste keuze heeft gemaakt, klik op de knop 'Ga naar vraag 2'. > ga naar vraag 2.

☐ ander land t.w.: > ga naar vraag 3

- 2. In welke gemeente en provincie bent u geboren?**

gemeente:

provincie:

3. In welk land is uw vader geboren?

 Nederland

☐ ander land t.w.:

4. In welk land is uw moeder geboren?

 Nederland

ander land t.w.:

5. Welke nationaliteit(en) heeft u nu?

(bij meer dan 1 nationaliteit deze noteren)

☐ Nederland

☐ anders t.w.:

niet invullen door patient

Registernummer: 1111

Registernummer:

(alleen indien ingevuld in IDENT. GEDEELTE)

Woonplaats: CBS code

Geslacht: ☐ ☐

Geb.datum: | | || | || | ddmmjj

Huisarts:

______ kode geb.land

UUUUUUUUUUU code geb.gemeente

|_|_|_| kode geb.land

|_|_|_| kode geb.land

U U U	kode nat.
-------	-----------

_____ kode nat.

P-V1.9-b

6. In welke gemeente(n) heeft u tot nu toe achtereenvolgens gewoond?

(s.v.p. achter elke gemeente binnen Nederland de provincie vermelden of indien de gemeente in het buitenland ligt de naam van het land vermelden. Verder de jaartallen vermelden van welk jaar tot welk jaar u daar gewoond heeft. Mocht u in méér dan 10 gemeenten hebben gewoond dan de laatste 10 vermelden.)

gemeente(n):	provincie / land	van welk jaar	tot welk jaar	kode gem.
1		119	119	
2		119	119	
3		119	119	
4		119	119	
5		119	119	
6		119	119	
7		119	119	
8		119	119	
9		119	119	
10		119	119	

niet invullen
door patient

7. Hoe lang woonde u in de regio Zuid-Limburg VÓÓRDAT u darmklachten had?

Wanneer u tussendoor perioden buiten Zuid-Limburg woonde, deze niet meetellen.
Zuid-Limburg strekt zich uit over alle gemeenten BENEDEN de gemeente Echt.

- ☐ korter dan 1 jaar
☐ 1 tot en met 5 jaar
☐ langer dan 5 jaar
☐ woon(de) alleen in Zuid-Limburg gedurende mijn studie-periode
☐ woonde buiten Zuid-Limburg

8. In welke gemeente(n) woonde u de laatste 5 jaren VÓÓRDAT u darmklachten had?

gemeente:	provincie:	
gemeente:	provincie:	
gemeente:	provincie:	

9. Wat is uw huidige burgerlijke staat?

- ☐ gehuwd of samenwonend
☐ ongehuwd
☐ gescheiden
☐ weduwe/weduwenaar

FAMILIE

1. Heeft u een tweelingbroer of -zus?

☐ nee → ga naar vraag 2

☐ ja → 1a. Is het van een eenelinge of van een twee-eiige?

1 ☐ eenelinge

2 ☐ twee-eiige

1b. Heeft uw tweelingbroer of -zus een chronische darmziekte-geschiedenis?

☐ nee

☐ ja → Welke en in welk jaar is die darmziekte als diagnose gesteld?

1 ☐ ziekte van Crohn

2 ☐ Colitis Ulcerosa

3 ☐ anders

4 ☐ weet niet

Gesteld in het jaar:

2. Hoeveel broers en/of zussen heeft u die ouder zijn dan uzelf?

Aantal:

3. Hoeveel broers en/of zussen heeft u die jonger zijn dan uzelf?

Aantal:

De volgende vragen gaan over chronische darmziekten te weten: de ziekte van Crohn, colitis ulcerosa, chronische proctitis (ontsteking laatste deel van de dikke darm) en chronische darmziekten van onbekende oorzaak.

De vragen gaarne zo volledig mogelijk invullen. Indien een antwoord niet bekend is dit ook noteren.

(Nu komen enkele vragen over uw eigen natuurlijke familie)

4. Komt chronische darmziekte voor in uw eigen (natuurlijke) familie?

Hierbij denken wij aan: vader, moeder, broers, zussen, neven, nichten, ooms, tantes.

Dus de 1e en 2e graads bloedverwantschap.

☐ nee → ga naar vraag 5

☐ weet niet

☐ ja → beantwoord dan de navolgende vragen over uw ouders, broers, zussen, kinderen, neven, nichten, ooms en tantes:

4a. Heeft uw vader en/of moeder een chronische darmziekte (gehad)?

VADER: ☐ nee

☐ weet niet

☐ ja

MOEDER: ☐ nee

☐ weet niet

☐ ja

→ ga naar vraag 4b

Welke diagnose werd gesteld?

☐ ziekte van Crohn

☐ Colitis Ulcerosa

☐ chronische proctitis

☐ andere chronische darmziekte

☐ onbekend

In welk jaar werd die diagnose gesteld?

In het jaar

In welk jaar is uw vader geboren?

In het jaar

Is uw vader nog in leven?

☐ nee

☐ ja

In welk jaar is hij gestorven?

In het jaar

Welke diagnose werd gesteld?

☐ ziekte van Crohn

☐ Colitis Ulcerosa

☐ chronische proctitis

☐ andere chronische darmziekte

☐ onbekend

In welk jaar werd die diagnose gesteld?

In het jaar

In welk jaar is uw moeder geboren?

In het jaar

Is uw moeder nog in leven?

☐ nee

☐ ja

In welk jaar is zij gestorven?

In het jaar

4b. In welk jaar zijn uw broers en zussen geboren; welke broer en/of zus had een darmziekte; in welk jaar werd die diagnose gesteld?

Hierbij begint u bij de oudste broer of zus en gaat zo het rijtje af tot de jongste. Uzelf niet vermelden.

Indien geen broers/zussen, ga naar vraag 4c

soort darmziekte: 1 = ziekte van Crohn
2 = Colitis Ulcerosa
3 = chronische proctitis
4 = andere chronische darmziekte
5 = onbekend
6 = geen

	geboren in het jaar	nog in leven	overleden --> in het jaar	soort darmziekte	de diagnose werd gesteld in het jaar
de oudste	119111	☐	☐	119111	119111
de 2e	119111	☐	☐	119111	119111
de 3e	119111	☐	☐	119111	119111
de 4e	119111	☐	☐	119111	119111
de 5e	119111	☐	☐	119111	119111
de 6e	119111	☐	☐	119111	119111
de 7e	119111	☐	☐	119111	119111
de 8e	119111	☐	☐	119111	119111
de 9e	119111	☐	☐	119111	119111
de 10e	119111	☐	☐	119111	119111

Nu komen enkele vragen over uw kinderen:

KINDEREN:

4c. Heeft u kinderen?

☐ nee --> ga naar vraag 5

☐ ja --> Hoeveel? Hierbij het aantal overleden kinderen meetellen.

111 kinderen

4d. In welk jaar zijn uw kinderen geboren; welk kind had een darmziekte; in welk jaar werd die diagnose gesteld?

Hierbij begint u bij uw oudste kind en gaat zo het rijtje af tot de jongste.

soort darmziekte: 1 = ziekte van Crohn
2 = Colitis Ulcerosa
3 = chronische proctitis
4 = andere chronische darmziekte
5 = onbekend
6 = geen

	geboren in het jaar	nog in leven	overleden --> in het jaar	soort darmziekte	de diagnose werd gesteld in het jaar
het oudste	119111	☐	☐	119111	119111
het 2e	119111	☐	☐	119111	119111
het 3e	119111	☐	☐	119111	119111
het 4e	119111	☐	☐	119111	119111
het 5e	119111	☐	☐	119111	119111
het 6e	119111	☐	☐	119111	119111
het 7e	119111	☐	☐	119111	119111
het 8e	119111	☐	☐	119111	119111
het 9e	119111	☐	☐	119111	119111
het 10e	119111	☐	☐	119111	119111

Nu komen vragen over uw echtgenoot/echtgenote/levenspartner. Indien u op dit moment ongehuwd of alleenstaand bent ga dan naar vraag 7. (Wel invullen indien u weduw(e)naar of gescheiden bent en kinderen uit dit huwelijk een chronische darmziekte hebben).

ECHTGENOOT/ECHTGENOTE/LEVENSPARTNER:

5. In welk jaar is uw echtgenoot/echtgenote/levenspartner geboren?

Indien geen echtgenoot/echtgenote/levenspartner, ga naar vraag 7 "FAMILIE IN DE TWEEDE GRAAD"

Echtgenoot/echtgenote/levenspartner is geboren in

Echtgenoot/echtgenote/levenspartner is: 1 ☐ nog in leven

2 ☐ overleden ----> in het jaar

6. Heeft/had uw echtgenoot/echtgenote/levenspartner een chronische darmziekte?

☐ nee

☐ ja ----->

☐ weet niet

Welke soort darmziekte? soort darmziekte:

1 = ziekte van Crohn
2 = Colitis Ulcerosa
3 = chronische proctitis
4 = andere chronische darmziekte
5 = onbekend
6 = geen

Nu komen vragen over uw familie in de tweede graad.

FAMILIE IN DE TWEEDE GRAAD:

Familie in de tweede graad omvat ooms en tantes (zijnde broers en zussen van ouders), neven en nichten (zijnde kinderen van deze ooms en tantes) en grootouders van vaders- en moederszijde.

7. Heeft familie in de 2e graad een chronische darmziekte en zoja hoeveel ooms, tantes, neven, nichten en/of grootouders hadden een chronische darmziekte?

☐ nee

☐ ja ----->

☐ weet niet

7a. Hoeveel ooms, tantes, neven, nichten en/of grootouders hadden welke chronische darmziekte(n)?

Ooms en tantes:

ziekte van Crohn

aantal:

Colitis Ulcerosa

chronische proctitis

andere chronische darmziekte

onbekend

neven en nichten:

ziekte van Crohn

Colitis Ulcerosa

chronische proctitis

andere chronische darmziekte

onbekend

grootouders:

ziekte van Crohn

Colitis Ulcerosa

chronische proctitis

andere chronische darmziekte

onbekend

De volgende vragen gaan over het vóórkomen van bepaalde vormen van chronische darmziekten en mogelijke complicaties bij uw eerstegraads familieleden.

8. Heeft iemand van uw eerstegraads familieleden (ouders, kinderen, broers of zussen) ooit een thrombosebeen/arm doorgemaakt?

Onder thrombosebeen/arm verstaan wij een bloedstolsel in een ader van een arm of een been.

- ☐ nee
☐ ja -----> Hoeveel eerstegraads familieleden? [] [] aantal
☐ weet niet

9. Heeft iemand van uw eerstegraads familieleden (ouders, kinderen, broers of zussen) ooit een longembolie doorgemaakt?

Onder longembolie verstaan wij een bloedstolsel in de vaten van de longen.

- ☐ nee
☐ ja -----> Hoeveel eerstegraads familieleden? [] [] aantal
☐ weet niet

10. Heeft iemand van uw eerstegraads familieleden (ouders, kinderen, broers of zussen) ooit een hartinfarct doorgemaakt?

- ☐ nee
☐ ja -----> Hoeveel eerstegraads familieleden? [] [] aantal
☐ weet niet

11. Heeft iemand van uw eerstegraads familieleden (ouders, kinderen, broers of zussen) ooit een herseninfarct doorgemaakt?

Onder herseninfarct verstaan wij een stolsel in de bloedvaten van de hersenen (ook wel een "hersen-attack", "CVA" of "TIA" genoemd)

- ☐ nee
☐ ja -----> Hoeveel eerstegraads familieleden? [] [] aantal
☐ weet niet

VOEDING

1. Heeft u zelf als baby borstvoeding gekregen?

- 1 ☐ nee
2 ☐ ja, korter dan 3 maanden
3 ☐ ja, langer dan 3 maanden
4 ☐ ja, weet niet hoelang
5 ☐ weet niet

- 2a. Volgde u in de jaren VÓÓRDAT de darmklachten ontstonden gedurende langere tijd een bepaald dieet of hield u zich aan een bepaald voedingspatroon of een alternatieve voedingsgewoonte?

- ☐ nee
☐ ja -----> Welk van de aangegeven voorbeelden is op u van toepassing?
(meerdere antwoorden mogelijk)

- dieet:
01 ☐ vetbeperkt dieet
02 ☐ diabetes mellitus (suikerziekte)
03 ☐ vezelarm dieet
04 ☐ cholesterol beperkt
05 ☐ ander dieet nl.:

- voedingspatroon:
06 ☐ Hindoeistaans
07 ☐ Kosher (joods)
08 ☐ Moslim

- alternatieve voedingsgewoonte:
09 ☐ macrobiotische voeding
10 ☐ vegetarisch (strikt)
11 ☐ vegetarisch (wel zuivelprodukten)

- overig:
12 ☐ anders nl.:

2b. Volgt u MOMENTEEL een dieet of houdt u zich MOMENTEEL aan een bepaald voedingspatroon of een alternatieve voedingsgewoonte?

Indien u minder dan 1 jaar darmklachten heeft is de periode hetzelfde als bij vraag 2a, dan deze vraag toch invullen)

☐ nee

☐ ja ----> Welk van de aangegeven voorbeelden is op u van toepassing?

(meerdere antwoorden mogelijk)

dieet:

01 ☐ vetbeperkt dieet

02 ☐ diabetes mellitus (suikerziekte)

03 ☐ vezelarm dieet

04 ☐ cholesterol beperkt

05 ☐ ander dieet nl.:

voedingspatroon:

06 ☐ Hindoeistaans

07 ☐ Kosher (Joods)

08 ☐ Moslim

alternatieve voedingsgewoonte:

09 ☐ macrobiotische voeding

10 ☐ vegetarisch (strikt)

11 ☐ vegetarisch (wel zuivelprodukten)

overig:

12 ☐ anders nl.:

3. Heeft u in verband met uw chronische darmziekte wel eens contact gehad met een diëtist(e)?

1 ☐ nee

2 ☐ ja, 1 of 2 keer

3 ☐ ja, vaker dan 2 keer

4. Gebruikte u gedurende het afgelopen jaar (buiten eventuele ziekenhuisopnames) vaker een vorm van vloeibare energieverrijkte bijvoeding? (zoals bv. Nutrison, Nutridrink of Fortimel)

☐ nee

☐ ja ----> gemiddeld [] [] dagen per maand (maand is hier 30 dagen)

5. Heeft u op het moment wanneer de chronische darmziekte aktiever is een duidelijk veranderd eetpatroon (hierdoor)?

☐ nee

☐ ja ----> 1 ☐ hoeveelheid duidelijk minder

2 ☐ hoeveelheid duidelijk meer

3 ☐ samenstelling duidelijk anders

4 ☐ hoeveelheid duidelijk minder en samenstelling anders

5 ☐ hoeveelheid duidelijk meer en samenstelling anders

6. Hoe vaak at u gemiddeld ingemaakt ("geweekt") voedsel PER MAAND in de 5 jaren VÓÓRDAT uw darmklachten ontstonden?

[] [] keer per maand

Nu komen een aantal vragen waarbij naar de periode van 5 jaar VÓÓRDAT de darmklachten ontstonden en naar het AFGELOPEN jaar wordt gevraagd. Indien u minder dan 1 jaar darmklachten heeft kan dit elkaar overlappen, toch a.u.b. beide invullen.

7. Hoeveel koppen koffie drinkt u gemiddeld PER DAG, met en/of zonder suiker?

	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
aantal koppen zonder suiker per dag	[] []	[] []
aantal koppen met suiker per dag	[] []	[] []

8. Hoeveel koppen thee drinkt u gemiddeld PER DAG, met of zonder suiker?

	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
aantal koppen zonder suiker per dag	<input type="text"/>	<input type="text"/>
aantal koppen met suiker per dag	<input type="text"/>	<input type="text"/>

9. HOEVAAK at u in de 5 jaren VÓÓRDAT de darmklachten begonnen een van de volgende soorten vis en hoevaak in het AFGELOPEN jaar? (het gemiddeld gebruik aankruisen)

soort vis	in de 5 jaren VÓÓRDAT gemiddeld gebruik:					in het AFGELOPEN jaar gemiddeld gebruik:				
	1 x per dag of meer	5-6 keer per week	2-4 keer per week	1 keer per week	minder dan 1 keer per week	1 x per dag of meer	5-6 keer per week	2-4 keer per week	1 keer per week	minder dan 1 keer per week
totale hoeveelheid vis	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
waarvan: magere vis (zoals bijvoorbeeld: baars, kabeljauw, schelvis, schol, snoekbaars, tarbot, tonijn, garnalen, mosselen, wijting, zeelt)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
gemiddeld vette vis (zoals bijvoorbeeld: bot, brasem, forel, heilbot, karper)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
vette vis (zoals bijvoorbeeld: ansjovis, sprout, zalm, paling, lekkerbekje, makreel, haring, bokking, vissticks)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

10. Hoeveel gram van de verschillende soorten vis at u ongeveer PER WEEK in de 5 jaar VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar?

(Een gemiddelde portie schol of kabeljauw bedraagt ongeveer 150 gram per keer)

	in de 5 jaren VÓÓRDAT hoeveelheid per week:	in het AFGELOPEN jaar hoeveelheid per week:
totale hoeveelheid vis	<input type="text"/> gram	<input type="text"/> gram
waarvan: magere vis (zoals bijvoorbeeld: baars, kabeljauw, schelvis, schol, snoekbaars, tarbot, tonijn, garnalen, mosselen, wijting, zeelt)	<input type="text"/> gram	<input type="text"/> gram
gemiddeld vette vis (zoals bijvoorbeeld: bot, brasem, forel, heilbot, karper)	<input type="text"/> gram	<input type="text"/> gram
vette vis (zoals bijvoorbeeld: ansjovis, sprout, zalm, paling, lekkerbekje, makreel, haring, bokking, vissticks)	<input type="text"/> gram	<input type="text"/> gram

11. At u wel eens citrusvruchten (sinaasappels, grapefruits, mandarijnen, citroenen enz.) in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel at u er dan gemiddeld PER WEEK?

aantal citrus- vruchten	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	<input type="text"/>	<input type="text"/>
2 - 5	<input type="text"/>	<input type="text"/>
6 - 10	<input type="text"/>	<input type="text"/>
11 - 15	<input type="text"/>	<input type="text"/>
16 - 20	<input type="text"/>	<input type="text"/>
meer dan 20	<input type="text"/>	<input type="text"/>

12. Dronk u wel eens cola in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel glazen dronk u dan gemiddeld PER WEEK?

aantal glazen	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	☐	☐
2 - 5	☐	☐
6 - 10	☐	☐
11 - 15	☐	☐
16 - 20	☐	☐
meer dan 20	☐	☐

13. Dronk u wel eens jus d'orange ("sinaasappelsap") in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel glazen dronk u dan gemiddeld PER WEEK?

aantal glazen	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	☐	☐
2 - 5	☐	☐
6 - 10	☐	☐
11 - 15	☐	☐
16 - 20	☐	☐
meer dan 20	☐	☐

14. At u wel eens kauwgum in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel stukjes at u dan gemiddeld PER WEEK?

aantal stukjes	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	☐	☐
2 - 5	☐	☐
6 - 10	☐	☐
11 - 15	☐	☐
16 - 20	☐	☐
meer dan 20	☐	☐

15. At u wel eens chocola (repen, marsen e.d.) in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel at u er dan gemiddeld PER WEEK?

aantal	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	☐	☐
2 - 5	☐	☐
6 - 10	☐	☐
11 - 15	☐	☐
16 - 20	☐	☐
meer dan 20	☐	☐

16. At u wel eens bonbons in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar? Indien u dit wel eens deed, hoeveel at u er dan gemiddeld PER WEEK?

aantal	in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
0 of 1	☐	☐
2 - 5	☐	☐
6 - 10	☐	☐
11 - 15	☐	☐
16 - 20	☐	☐
meer dan 20	☐	☐

BEROEP

Wij stellen u nu enkele vragen over uw beroep in de periode "VOÓRDAT" u chronische darmklachten kreeg en over de "huidige" periode. Ook als de situatie gelijk is toch gaarne beide periodes invullen.

VOÓRDAT u chronische darmziekte kreeg:

1. Had u betaald werk voordat u chronische darmziekte kreeg?

- 1 ☐ ja, in loondienst
2 ☐ ja, als zelfstandige
3 ☐ ja, als meewerkende in gezinsbedrijf
4 ☐ wel onbetaald werk
5 ☐ nee -----> ga door naar vraag 6

2. Gaf u daarbij leiding aan werknemers?

- 1 ☐ nee, ik geef/gaf geen leiding aan werknemers
2 ☐ ja, aan 1 tot en met 10 werknemers
3 ☐ ja, aan 11 tot en met 24 werknemers
4 ☐ ja, aan 25 en meer werknemers

3. Wat was uw beroep?

Het beroep gaarne ruim omschrijven

.....
.....
.....

4. Werkte u toen full-time of part-time?

Full-time is 32 uur of meer per week,
Part-time is minder dan 32 uur per week

- 1 ☐ full-time
2 ☐ part-time

5. Hoeveel jaar had u toen full-time en/of part-time betaald werk gehad?

Full-time is 32 uur of meer per week, Part-time is minder dan 32 uur per week

Beide antwoorden invullen indien van toepassing.

Full-time

Part-time

6. Als u in het jaar voordat uw darmklachten begonnen geen beroep uitoefende wat was dan op u van toepassing?

- 1 ☐ was scholier/student
2 ☐ werkte in huishouden
3 ☐ was werkloos/werkzoekend/wachtgeld
4 ☐ was gepensioneerd, AOW, AWW, VUT
5 ☐ was in de WAO, AAW
6 ☐ was in de ziektewet
7 ☐ overig (bv. dienstplichtig, vrijwilligerswerk)
tw.

7. Wat was het beroep van uw partner? Voor kinderen hier het beroep van vader of moeder noteren. Het beroep gaarne ruim omschrijven.

.....
.....
.....

Dit beroep is van: ☐ partner
☐ vader of moeder

HUIDIGE situatie:

1. Heeft u momenteel betaald werk?

- 1 ☐ ja, in loondienst
2 ☐ ja, als zelfstandige
3 ☐ ja, als meewerkende in gezinsbedrijf
4 ☐ wel onbetaald werk
5 ☐ nee -----> ga door naar vraag 6

2. Geeft u daarbij leiding aan werknemers?

- 1 ☐ nee, ik geef geen leiding aan werknemers
2 ☐ ja, aan 1 tot en met 10 werknemers
3 ☐ ja, aan 11 tot en met 24 werknemers
4 ☐ ja, aan 25 en meer werknemers

3. Wat is uw huidige beroep?

Het beroep gaarne ruim omschrijven

.....
.....
.....

4. Werkt u momenteel full-time of part-time?

Full-time is 32 uur of meer per week,
Part-time is minder dan 32 uur per week

- 1 ☐ full-time
2 ☐ part-time

5. Hoeveel jaar heeft u momenteel full-time en/of part-time betaald werk?

Full-time is 32 uur of meer per week, Part-time is minder dan 32 uur per week

Beide antwoorden invullen indien van toepassing.

Full-time

Part-time

6. Als u momenteel geen beroep uitoefent wat is dan op u van toepassing?

- 1 ☐ ben scholier/student
2 ☐ werk in huishouden
3 ☐ ben werkloos/werkzoekend/wachtgeld
4 ☐ ben gepensioneerd, AOW, AWW, VUT
5 ☐ ben in de WAO, AAW
6 ☐ ben in de ziektewet
7 ☐ overig (bv. dienstplichtig, vrijwilligerswerk)
tw.

7. Wat is het huidige beroep van uw partner? Voor kinderen hier het beroep van vader of moeder noteren. Het beroep gaarne ruim omschrijven.

.....
.....
.....

Dit beroep is van: ☐ partner
☐ vader of moeder

OPLEIDING

1. Wat is de hoogst voltooide opleiding van uzelf en van uw eventuele partner?

Kruis het meest toepasselijke aan

uzelf	partner	opleiding:	
☐	☐	1 Lager algemeen onderwijs:	basisonderwijs, of een gedeelte hiervan
☐	☐	2 Lager beroepsonderwijs:	omvat o.a.: LTS (lagere technische school), LHNO (lager huishoud- en nijverheidsonderwijs), landbouwhuishoud-onderwijs, huishoudschool, vakschool voor meisjes, nijverheidsschool, LEAO, detailhandels(vak)school, lager nautisch onderwijs, etc.
☐	☐	3 Middelbaar algemeen onderwijs:	omvat o.a.: LAVO, VGLO, ULO, MULO, MAVO-3, MAVO-4, 3-jarige HBS, middenschool, 3 jaar HAVO
☐	☐	4 Middelbaar beroepsonderwijs:	omvat o.a.: MTS, UTS, MBA, MEAO, middelbare landbouw- en tuinbouwschool, praktijkdiploma boekhouden, ULHNO, MHNO, MSPO, kleuterweekschool (opleiding tot kleuterleidster), horecaschool, middelbaar middenstandsonderwijs, verpleegstersopleiding, horlogemakersvakschool, NIMA-A, etc.
☐	☐	5 Voortgezet algemeen onderwijs:	omvat o.a.: 5-jarige HBS, MMS, gymnasium, lyceum, atheneum, HAVO
☐	☐	6 Hoger beroepsonderwijs:	omvat o.a.: HTS, HEAO, Sociale Academie, Politie Academie, Pedagogische Academie, Kweekschool, hoger kunstonderwijs, Hogere Zeevaartschool, SPD, LO-Akten, HHNO, HSPO, diëtiste opleiding, huishoudkundige, logopedie, mondhygiëniste-opleiding, leraressen opleiding, MO-A, MO-C, Hogere Hotelschool, Hogere Detail-handelsschool, NIMA B/C, Nijenrode, AMBI, ingenieursfase nieuwe stijl, GA-II, HBOV etc.
☐	☐	7 Hoger algemeen onderwijs:	omvat o.a.: kandidaatsexamen oude stijl, doctoraal examen nieuwe stijl
☐	☐	8 Wetenschappelijk onderwijs:	omvat o.a.: doctoraalfase oude stijl, ingenieursfase oude stijl, promotie (dr.), NIVRA (slotfase), actuaire, MO-B, Hogere Krijgsschool

2. Studeert u nog of volgt u nog een beroepsopleiding?

- ☐ nee
- ☐ ja -----> Hoeveel jaar hiervan heeft u reeds voltooid?
- [] jaar

ZIEKTE / LICHAAMELIJKE KLACHTEN EN MEDICIJNEN

1. In welk jaar kreeg u de eerste darmklachten?

In het jaar ----> Weet u ook nog (ongeveer) in welke maand van dat jaar?

01 ☐ januari	07 ☐ juli
02 ☐ februari	08 ☐ augustus
03 ☐ maart	09 ☐ september
04 ☐ april	10 ☐ oktober
05 ☐ mei	11 ☐ november
06 ☐ juni	12 ☐ december

2. In welk jaar bent u hiermee voor het eerst naar de HUISARTS gegaan?

In het jaar ----> Weet u ook nog (ongeveer) in welke maand van dat jaar?

01 ☐ januari	05 ☐ mei	09 ☐ september
02 ☐ februari	06 ☐ juni	10 ☐ oktober
03 ☐ maart	07 ☐ juli	11 ☐ november
04 ☐ april	08 ☐ augustus	12 ☐ december

3. In welk jaar bent u hiermee voor het eerst naar de arts gegaan die de diagnose heeft gesteld (vaststelling van de aard van de ziekte)?

In het jaar ----> Weet u ook nog (ongeveer) in welke maand van dat jaar?

01 ☐ januari	05 ☐ mei	09 ☐ september
02 ☐ februari	06 ☐ juni	10 ☐ oktober
03 ☐ maart	07 ☐ juli	11 ☐ november
04 ☐ april	08 ☐ augustus	12 ☐ december

4. In welk jaar is bij u de diagnose ten aanzien van de darmklachten gesteld?

In het jaar ----> Weet u ook nog (ongeveer) in welke maand van dat jaar?

01 ☐ januari	05 ☐ mei	09 ☐ september
02 ☐ februari	06 ☐ juni	10 ☐ oktober
03 ☐ maart	07 ☐ juli	11 ☐ november
04 ☐ april	08 ☐ augustus	12 ☐ december

5. Wat was uw gewicht + lengte vóórdat uw darmklachten begonnen en in welk jaar was dat?

gewicht: kg lengte: cm jaartal:
 weet niet: ☐ weet niet: ☐

6. Wat is uw huidige gewicht? gewicht: kg weet niet: ☐

7. Hoeveel weken heeft u het afgelopen jaar niet kunnen werken of niet naar school kunnen gaan i.v.m. darmziekten? weken

8. Heeft de darmziekte u belemmerd in uw opleiding, in uw werk, in uw vrije tijd?

In opleiding	In werk	In vrije tijd
1 ☐ nee	1 ☐ nee	1 ☐ nee
2 ☐ ja	2 ☐ ja	2 ☐ ja
3 ☐ geen mening	3 ☐ geen mening	3 ☐ geen mening

9. Bent u momenteel in de ziektewet in verband met darmziekten of door andere reden?

- 1 ☐ nee
 2 ☐ ja, in verband met darmziekten
 3 ☐ ja, door andere reden

10. Bent u momenteel in de WAO in verband met darmziekten of door andere reden?

- 1 ☐ nee
 2 ☐ ja, in verband met darmziekten
 3 ☐ ja, door andere reden

11. Kunt u momenteel geen school volgen i.v.m. darmziekten of andere reden?

- 1 ☐ nee
 2 ☐ ja, in verband met darmziekten
 3 ☐ ja, door andere reden
 4 ☐ niet van toepassing

12. Hoe vaak en hoelang bent u het afgelopen jaar in het ziekenhuis opgenomen?

- 1 ☐ geen opname (0|0|0) aantal dagen
2 ☐ 1 opname / totaal duur in dagen ----> () aantal dagen
3 ☐ 2 opnamen / totaal duur in dagen ----> () aantal dagen
4 ☐ 3 opnamen / totaal duur in dagen ----> () aantal dagen
5 ☐ 4 en meer opnamen / totaal duur in dagen () aantal dagen

13. Bent u geopereerd aan uw blindedarm?

- ☐ nee
☐ ja ----> Hoelang is dat geleden?
1 ☐ 0 t/m 4 jaar
2 ☐ 5 t/m 14 jaar
3 ☐ 15 t/m 24 jaar
4 ☐ 25 jaar en langer

14. Bent u geopereerd aan uw keelamandelen en/of neusamandelen ("amandelen geknipt")?

- ☐ nee
☐ ja ----> Hoelang is dat geleden?
1 ☐ 0 t/m 4 jaar
2 ☐ 5 t/m 14 jaar
3 ☐ 15 t/m 24 jaar
4 ☐ 25 jaar en langer

15. Had u GEWRICHTSKLACHTEN in de 3 maanden voordat u de eerste keer een arts raadpleegde wegens de darmklachten?

- 1 ☐ nee
2 ☐ ja
3 ☐ weet niet

Nu komen enkele vragen over zogenaamde allergische ziekten ("overgevoeligheids" ziekten)

16. Heeft u als baby dauwworm gehad?

Dauwworm is een eczeem (huiduitslag) bij zuigelingen voornamelijk op het behaarde hoofd en op de wangen voorkomend)

- 1 ☐ nee
2 ☐ ja
3 ☐ weet niet

17. Heeft u als kind of op latere leeftijd eczeem gehad (huiduitslag)?

- 1 ☐ nee
2 ☐ ja
3 ☐ nog steeds eczeem
4 ☐ weet niet

18. Heeft u als kind of op latere leeftijd hooikoorts gehad?

- 1 ☐ nee
2 ☐ ja
3 ☐ nog steeds hooikoorts
4 ☐ weet niet

19. Heeft u als kind of op latere leeftijd asthma gehad?

- 1 ☐ nee
2 ☐ ja
3 ☐ nog steeds asthma
4 ☐ weet niet

20. Heeft u andere allergische ziektebeelden (te maken hebbend met overgevoeligheid) of heeft u die gehad?

- ☐ nee
☐ ja, namelijk

De volgende vragen over "de Pil" / Orale anticonceptie en menopauze alleen door vrouwen beantwoorden.

Pil / Orale anticonceptie en menopauze:

1. Heeft u de menopauze bereikt/bent u in de overgang (geweest)?

☐ nee

☐ ja, ik bereikte mijn menopauze op mijn ____ leeftijdsjaar

2. Gebruikt u of heeft u ooit "de pil" (orale anticonceptie) gebruikt?

☐ nee, nooit -----> ga naar **ROKEN** op de volgende pagina

☐ ja -----> Beantwoord de volgende vragen:

2a. Gebruikte u de pil op het moment dat de darmziekte werd vastgesteld?

☐ nee

☐ ja

2b. Was u reeds met de pil gestopt op het moment dat de darmziekte werd vastgesteld?

☐ nee

☐ ja

2c. Welk(e) soort(en) gebruikte u in de jaren voorafgaand aan de eerste verschijnselen van uw darmziekte?

(Gaarne zo precies mogelijk vermelden)

soort:	periode		bij onderbreking eventueel	
	van:	tot:	2e periode vermelden	
			van:	tot:
☐ éénfase pil (normaal)	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _
☐ éénfase pil (mini pil)	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _
☐ tweefase pil (combinatie pil)	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _
☐ driefase pil (combinatie pil)	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _
☐ "prikpil" (spuit)	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _
☐ weet niet (meer) welk merk	1 9 _ _	1 9 _ _	1 9 _ _	1 9 _ _

2d. Hoeveel jaar heeft u de pil gebruikt voordat u darmklachten kreeg?

|_|_| aantal jaren

2e. Hoeveel jaar heeft u de pil in totaal gebruikt tot nu toe?

|_|_| aantal jaren

ROKEN

1. Heeft u ooit gerookt?

- ☐ nee -----> ga naar vraag 7
☐ ja

2. Gedurende welke periode(n) heeft u gerookt?

van tot

van tot

van tot

van tot

3. Wat rookt(e) u, sigaren, sigaretten en/of pijp? (kombinaties is mogelijk)

- 1 ☐ sigaren
 2 ☐ sigaretten
 3 ☐ pijp

4. Rookt u nog steeds?

- ☐ nee -----> 4a. Hoeveel jaren heeft u gerookt?
☐ ja ---> ga naar vraag 5 aantal jaren

4b. In welk jaar bent u definitief gestopt met roken?

In definitief gestopt

GA NAAR VRAAG 6

5. Hoeveel rookt u aan sigaretten, pijp en/of sigaren?

Sigaretten:

- 1 ☐ geen
 2 ☐ 0 - 9 per dag
 3 ☐ 10 - 19 per dag
 4 ☐ 20 - 39 per dag
 5 ☐ 40 en meer per dag

Pijptabak:

- 1 ☐ geen
 2 ☐ minder dan 50 gram per week
 3 ☐ meer dan 50 gram per week

Sigaren:

- 1 ☐ geen
 2 ☐ minder dan 5 per week
 3 ☐ meer dan 5 per week

6. Hoeveel rookte u gemiddeld in de tien jaar voorafgaand aan uw eerste darmklachten aan sigaretten, pijp en/of sigaren?

Sigaretten:

- 1 ☐ geen
 2 ☐ 0 - 9 per dag
 3 ☐ 10 - 19 per dag
 4 ☐ 20 - 39 per dag
 5 ☐ 40 en meer per dag

Pijptabak:

- 1 ☐ geen
 2 ☐ minder dan 50 gram per week
 3 ☐ meer dan 50 gram per week

Sigaren:

- 1 ☐ geen
 2 ☐ minder dan 5 per week
 3 ☐ meer dan 5 per week

7. Hoeveel personen in uw gezin rookten dagelijks in de jaren voorafgaand aan uw darmziekte? (Uzelf niet meetellen)

- 1 ☐ geen
 2 ☐ één
 3 ☐ twee of meer

8. Vertoefde u dagelijks in een rokerige omgeving (in uw gezin of op uw werkplek) in de jaren voorafgaande aan uw darmziekte?

- ☐ nee
☐ ja

1. Heeft u naar uw mening voldoende informatie gehad van de arts over de onderzoeken die uitgevoerd werden om een diagnose te stellen over uw darmklachten?

- bijvoorbeeld: over het onderwerp voeding informatie gewenst van de diëtiste en van de huisarts*

onderwerpen: nee ja ----> zoja, informatie gewenst van:

[illegible]

onderwerpen: nee ja ----> zoja, informatie gewenst van:

1 voeding	☐	☐	☐	☐	☐
2 medikatie	☐	☐	☐	☐	☐
3 ziektebeeld	☐	☐	☐	☐	☐
4 emotionele verwerking	☐	☐	☐	☐	☐
5 patiëntenvereniging	☐	☐	☐	☐	☐
6	☐	☐	☐	☐	☐

informatie van:

1 = diëtiste
2 = wijkverpleegkundige
3 = huisarts
4 = specialist
5 = patiëntenvereniging
6 = psycholoog
7 = geen van genoemden

1. Voelde u zich serieus genomen met betrekking tot uw klachten VÓÓRDAT de diagnose chronische darmziekte werd gesteld? (meer antwoorden mogelijk)

- 1 ☐ nee -----> met name niet door: 1 ☐ arts
2 ☐ ja 2 ☐ partner
3 ☐ geen mening 3 ☐ overige familie
4 ☐ op het werk
5 ☐ op school

2. Voelde u zich goed opgevangen met betrekking tot uw klachten VÓÓRDAT de diagnose chronische darmziekte werd gesteld? (meer antwoorden mogelijk)

- 1 ☐ nee -----> met name niet door: 1 ☐ arts
2 ☐ ja 2 ☐ partner
3 ☐ geen mening 3 ☐ overige familie
4 ☐ op het werk
5 ☐ op school

3. Voelde u zich goed opgevangen met betrekking tot uw klachten de eerste tijd NÁDAT de diagnose chronische darmziekte werd gesteld? (meer antwoorden mogelijk)

- 1 ☐ nee -----> met name niet door: 1 ☐ arts
2 ☐ ja 2 ☐ partner
3 ☐ geen mening 3 ☐ overige familie
4 ☐ op het werk
5 ☐ op school

OVERIG

1. Heeft u als kind gedurende langere tijd (meer dan 5 jaar) een troeteldier gehad?
- 1 ☐ nee
2 ☐ ja
3 ☐ weet niet
2. Heeft u als kind langdurig (meer dan 2 jaar) een speen gebruikt?
- 1 ☐ nee
2 ☐ ja
3 ☐ weet niet
3. Heeft u het idee dat u duidelijk later dan uw leeftijdgenoten in de puberteit kwam?
(bijvoorbeeld bij jongens het later ontstaan van baardgroei en stemverandering en
bijvoorbeeld bij meisjes het later ontstaan van borstontwikkeling en eerste menstruatie)
- 1 ☐ nee
2 ☐ ja
3 ☐ weet niet
4. Heeft u een kunstgebit (prothese)?
- ☐ nee
☐ ja -----> Sinds welk jaar?
sinds
5. Hoeveel amalgaam-vullingen (grijze) heeft u in uw gebit?
- aantal ☐ weet niet
6. Op welke leeftijd ongeveer kreeg u de eerste (amalgaam)vulling in uw tanden?
- Toen ik jaar oud was. ☐ weet niet ☐ niet van toepassing
7. Hoe vaak poetste u uw tanden met tandpasta in de 5 jaren VÓÓRDAT de darmklachten begonnen en in het AFGELOPEN jaar?
in de 5 jaren VÓÓRDAT	in het AFGELOPEN jaar
01 ☐ meer dan 3 keer per dag	01 ☐ meer dan 3 keer per dag
02 ☐ 3 x per dag	02 ☐ 3 x per dag
03 ☐ 2 - 3 x per dag	03 ☐ 2 - 3 x per dag
04 ☐ 2 x per dag	04 ☐ 2 x per dag
05 ☐ 1 - 2 x per dag	05 ☐ 1 - 2 x per dag
06 ☐ 1 x per dag	06 ☐ 1 x per dag
07 ☐ 5 - 6 x per week	07 ☐ 5 - 6 x per week
08 ☐ 2 - 4 x per week	08 ☐ 2 - 4 x per week
09 ☐ minder dan 1 x per week	09 ☐ minder dan 1 x per week
10 ☐ nooit	10 ☐ nooit
8. Bent u naar uw eigen mening ambitieus/prestigeus?
- 1 ☐ nee
2 ☐ ja
3 ☐ geen mening
9. Ondervond u in de jaren voorafgaand aan de eerste klachten van uw darmziekte veel psychische stress bij het uitoefenen van uw beroep of het volgen van een opleiding?
- 1 ☐ nee
2 ☐ ja
3 ☐ geen mening
4 ☐ niet van toepassing
10. Denkt u dat spanningen bij u mede oorzaak zijn van het ontstaan van uw darmziekte?
- 1 ☐ nee
2 ☐ ja
3 ☐ geen mening

11. Hoe vindt u over het algemeen uw gezondheid?

- 1 ☐ zeer slecht
 2 ☐ slecht
 3 ☐ matig
 4 ☐ goed
 5 ☐ zeer goed

12. Heeft de ziekte u belemmerd in de relatie met uw levenspartner?

- 1 ☐ nee
 2 ☐ ja
 3 ☐ geen mening
 4 ☐ niet van toepassing

KWALITEIT VAN LEVEN

De volgende vragen zijn opgenomen om een idee te krijgen hoe u zich gedurende de afgelopen twee weken heeft gevoeld. Er wordt gevraagd naar klachten die kunnen behoren bij uw darmziekte, maar ook zijn vragen opgenomen over algemeen welbevinden en stemming. Telkens het meest toepasselijke antwoord aankruisen.

1. Hoe vaak heeft u in de afgelopen twee weken ontlasting gehad in vergelijking met een rustige fase van uw darmziekte?

- 1 ☐ ontlasting vaker dan ooit
 2 ☐ extreem vaak
 3 ☐ erg vaak
 4 ☐ matige verhoging in vergelijking met rustige fase
 5 ☐ enige verhoging in vergelijking met rustige fase
 6 ☐ lichte verhoging in vergelijking met rustige fase
 7 ☐ geen verhoging van aantal malen ontlasting

	de hele tijd	grootste deel van de tijd	een groot deel van de tijd	een matig deel van de tijd	een klein deel van de tijd	bijna geen deel van de tijd	helemaal niet
2. Hoe vaak was moeheid of het gevoel "uitgeblust te zijn" de afgelopen twee weken voor u een probleem?	☐	☐	☐	☐	☐	☐	☐
3. Hoe vaak was u de afgelopen twee weken gefrustreerd, ongeduldig of rusteloos?	☐	☐	☐	☐	☐	☐	☐
4. Hoe vaak heeft u de afgelopen twee weken school moeten missen of vrij moeten nemen van uw werk als gevolg van darmproblemen?	☐	☐	☐	☐	☐	☐	☐
5. Hoe vaak heeft u de afgelopen twee weken dunne ontlasting gehad?	☐	☐	☐	☐	☐	☐	☐
6. Hoe vaak bent u in de afgelopen twee weken ongerust geweest over een eventueel noodzakelijke operatie voor uw darmziekte?	☐	☐	☐	☐	☐	☐	☐
7. Hoe vaak heeft u de afgelopen twee weken een afspraak moeten afzeggen of uitstellen in verband met uw darmziekte?	☐	☐	☐	☐	☐	☐	☐
8. Hoe vaak heeft u de afgelopen twee weken last gehad van buikkrampen?	☐	☐	☐	☐	☐	☐	☐

	de hele tijd	grootste deel van de tijd	een groot deel van de tijd	een matig deel van de tijd	een klein deel van de tijd	bijna geen deel van de tijd	helemaal niet
9. Hoe vaak heeft u zich de afgelopen twee weken niet lekker gevoeld ("algemeen onwel zijn")	☐	☐	☐	☐	☐	☐	☐
10. Hoe vaak heeft u zich de afgelopen twee weken zorgen gemaakt om niet op tijd bij een toilet te kunnen komen?	☐	☐	☐	☐	☐	☐	☐
11. Hoe vaak heeft u de afgelopen twee weken last gehad van buikpijn?	☐	☐	☐	☐	☐	☐	☐
12. Hoe vaak heeft u gedurende de afgelopen twee weken problemen gehad een goede nachtrust te krijgen of werd u 's nachts steeds wakker?	☐	☐	☐	☐	☐	☐	☐
13. Hoe vaak voelde u zich de afgelopen twee weken depressief of teneergeslagen?	☐	☐	☐	☐	☐	☐	☐
14. Hoe vaak heeft u de afgelopen twee weken gelegenheden vermeden waarvan u niet zeker wist dat er een toilet in de buurt was?	☐	☐	☐	☐	☐	☐	☐
15. Hoe vaak heeft u gedurende de afgelopen twee weken last gehad van windrigheid?	☐	☐	☐	☐	☐	☐	☐
16. Hoe vaak heeft u zich de afgelopen twee weken zorgen gemaakt over het behouden of verkrijgen van het gewicht dat u nastreeft?	☐	☐	☐	☐	☐	☐	☐
17. Veel patienten met chronische darmziekte maken zich vaak zorgen of hebben angsten die te maken hebben met hun ziekte. Onder andere zorgen om kanker te krijgen, zich nooit beter te voelen en angsten om weer veel last van hun darmziekte te krijgen. Hoe vaak heeft u dergelijke zorgen gehad gedurende de afgelopen twee weken?	☐	☐	☐	☐	☐	☐	☐
18. Hoe vaak heeft u gedurende de afgelopen twee weken last gehad van een opgeblazen gevoel?	☐	☐	☐	☐	☐	☐	☐
19. Hoe vaak heeft u de afgelopen twee weken last gehad van bloedverlies bij de ontlasting?	☐	☐	☐	☐	☐	☐	☐
20. Hoe vaak heeft u zich gedurende de afgelopen twee weken opgelaten gevoeld door uw darmprobleem?	☐	☐	☐	☐	☐	☐	☐
21. Hoe vaak heeft u de afgelopen twee weken het gevoel gehad dat u naar de toilet moest gaan waarbij dan echter geen ontlasting kwam?	☐	☐	☐	☐	☐	☐	☐
22. Hoe vaak heeft u zich de afgelopen twee weken verdrietig of van streek gevoeld?	☐	☐	☐	☐	☐	☐	☐
23. Hoe vaak heeft u zich de afgelopen twee weken kwaad gemaakt vanwege uw darmziekte?	☐	☐	☐	☐	☐	☐	☐

	de hele tijd	grootste deel van de tijd	een groot deel van de tijd	een matig deel van de tijd	een klein deel van de tijd	bijna geen deel van de tijd	helemaal niet
	1	2	3	4	5	6	7
24. Hoe vaak heeft u zich gedurende de afgelopen twee weken doodziek gevoeld?	☐	☐	☐	☐	☐	☐	☐
25. Hoe vaak was u gedurende de afgelopen twee weken geïrriteerd?	☐	☐	☐	☐	☐	☐	☐
26. Hoeveel energie had u de afgelopen twee weken?							
1 ☐ totaal geen energie							
2 ☐ heel erg weinig energie							
3 ☐ weinig energie							
4 ☐ enige energie							
5 ☐ matige hoeveelheid energie							
6 ☐ veel energie							
7 ☐ zeer veel energie							
27. Hoeveel moeite heeft het u de afgelopen twee weken gekost, door uw darmproblemen, om tijd te besteden aan ontspanning of sport?							
1 ☐ zeer veel moeite, ontspanning en sport waren niet mogelijk							
2 ☐ veel moeite							
3 ☐ best wel moeite							
4 ☐ enige moeite							
5 ☐ weinig moeite							
6 ☐ praktisch geen moeite							
7 ☐ helemaal geen moeite, geen beperking van sport/ontspanning door darmproblemen							
28. Hoe vaak heeft u zich gedurende de afgelopen twee weken relaxed en ontspannen gevoeld?							
1 ☐ nooit							
2 ☐ een klein deel van de tijd							
3 ☐ enig deel van de tijd							
4 ☐ een matig deel van de tijd							
5 ☐ grootste deel van de tijd							
6 ☐ bijna de hele tijd							
7 ☐ de hele tijd							
29. Hoe groot was het probleem voor u gedurende de afgelopen twee weken dat per ongeluk wat ontlasting werd verloren?							
1 ☐ een ernstig probleem							
2 ☐ een belangrijk probleem							
3 ☐ een matig probleem							
4 ☐ enige last							
5 ☐ weinig last							
6 ☐ bijna geen last							
7 ☐ geen last							
30. In welke mate hebben uw darmprobleem gedurende de afgelopen twee weken ertoe bijgedragen dat er een beperking was in uw seksuele leven?							
1 ☐ geen seksuele activiteit door darmproblemen							
2 ☐ zeer grote beperking door darmproblemen							
3 ☐ grote beperking door darmproblemen							
4 ☐ matige beperking door darmproblemen							
5 ☐ enige beperking door darmproblemen							
6 ☐ nauwelijks beperking door darmproblemen							
7 ☐ geen beperking door darmproblemen							

31. Hoe vaak had u gedurende de afgelopen twee weken het gevoel niet door uw omgeving begrepen te worden?

- 1 ☐ de hele tijd
- 2 ☐ bijna de hele tijd
- 3 ☐ grootste deel van de tijd
- 4 ☐ een matig deel van de tijd
- 5 ☐ enig deel van de tijd
- 6 ☐ een klein deel van de tijd
- 7 ☐ nooit

32. Hoe tevreden, gelukkig of zelfvoldaan was u gedurende de afgelopen twee weken met uzelf?

- 1 ☐ zeer ontevreden, grootste deel van de tijd ongelukkig
- 2 ☐ over het algemeen ontevreden, ongelukkig
- 3 ☐ iets ontevreden, ongelukkig
- 4 ☐ over het algemeen gelukkig, voldaan
- 5 ☐ tevreden, meeste deel van de tijd gelukkig
- 6 ☐ zeer tevreden, meeste deel van de tijd gelukkig
- 7 ☐ extreem tevreden, kon niet gelukkiger of meer voldaan zijn

HARTELIJK DANK VOOR UW MEDEWERKING

Opmerkingen:

.....

.....

.....

.....

.....

Appendix 3

MEDISCH FORMULIER®

Medisch Formulier IBD 1.0. All rights reserved.

IDENTIFIKATIE GEDEELTE: naw en postcode altijd invullen

Naam:
Voornamen:
Adres:
Postcode: [][][][][][] Woonplaats:
Geslacht : Geboortedatum: [][][][][][]
Huisarts:
Specialist: Specialisme:
Ziekenhuis:

KODERINGEN: ROLODEXMEDEWERKER

Registernummer: [][][][]

Invuldatum formulier [][][][][][] d d m m j j

Betreft de periode van [][][][][][] d d m m j j

Betreft de periode tot [][][][][][] d d m m j j

STATUS IN IBD-REGISTER INVULLEN DOOR ONDERZOEKER

1. Is de patiënt in de afgelopen periode overleden?

1 ☐ nee

2 ☐ ja -> datum: [][][][][][] d d m m j j

oorzaak:

2. Is de patiënt in de afgelopen periode verhuisd naar buiten de regio?

1 ☐ nee

2 ☐ ja -> nieuwe relevante gegevens
vermeld in het identifikatie gedeelte

3. Is de patiënt in de afgelopen periode uit behandeling gegaan van de aanmeldende arts, behalve als gevolg van overlijden?

1 ☐ nee

2 ☐ ja -> onder behandeling gekomen van:
(vermelden in identifikatie gedeelte)

1 ☐ (andere) huisarts

2 ☐ een specialist buiten de regio

3 ☐ een specialist binnen de regio

Registernummer: [][][][]

Alleen invullen indien identifikatie gedeelte is ingevuld

Woonplaats: [][][][]

Geslacht: []

Geboortedatum: [][][][][][] d d m m j j

Huisarts: [][][]

Specialist: [][][]

Specialisme: [][]

Ziekenhuiskode: [][][]

Doodsoorzaak: [][][] ICD-9

Door hoofdonderzoeker in te vullen

☐ speciale attentie voor hoofdonderzoeker

☐ door hoofdonderzoeker gezien

ZIEKENHUISOPNAMEN

1. Opnameperiode(n) in ziekenhuis gerelateerd aan chronische darmziekte gedurende 1e half jaar na 1e consult?

1 ☐ nee

2 ☐ ja -> opnamedatum ontslagdatum (ddmmjj)

9 ☐ onbekend

Indien de patiënt al/nog is opgenomen dan alleen opnamedatum vermelden en bij de ontslagdatum 9's invullen.

ANAMNESE

1. Duur van de klachten voorafgaand aan 1e consult?

____ aantal maanden

9 ☐ onbekend

Vragen 2 tot en met 6 gaan over de 3 maanden voorafgaand aan 1e consult

2. Frequentie defaecatie

1 ☐ < 1 maal per dag
2 ☐ 1 t/m 3 maal per dag
3 ☐ 4 t/m 7 maal per dag
4 ☐ > 8 maal per dag
9 ☐ onbekend

Consistentie

1 ☐ normaal
2 ☐ brijig
3 ☐ waterig
9 ☐ onbekend

Bloedbijmenging

1 ☐ nee
2 ☐ ja
9 ☐ onbekend

Slijmbijmenging

1 ☐ nee
2 ☐ ja
9 ☐ onbekend

3. Buikpijn?

1 ☐ nee

2 ☐ ja -> mate van buikpijn

1 ☐ weinig
2 ☐ matig
3 ☐ ernstig
9 ☐ onbekend

Type buikpijn

1 ☐ intermitterend
2 ☐ continu aanwezig
9 ☐ onbekend

Lokalisatie buikpijn
(meer antwoorden mogelijk)

1 ☐ diffuus
2 ☐ rechter onder quadrant
3 ☐ linker onder quadrant
4 ☐ rechter boven quadrant

5 ☐ linker boven quadrant
6 ☐ centraal
9 ☐ onbekend

4. Gewichtsverlies?

- 1 ☐ nee
 2 ☐ ja $\longrightarrow$ 1 ☐ 1 t/m 2 kg
 2 ☐ 3 t/m 5 kg
 3 ☐ 6 t/m 9 kg
 4 ☐ ≥ 10 kg
- 9 ☐ onbekend

5. Koorts? (> 38 graden C)

- 1 ☐ nee
 2 ☐ ja
 9 ☐ onbekend

6. Moeheid?

- 1 ☐ nee
 2 ☐ ja
 9 ☐ onbekend

Vragen 7 tot en met 10 bestrijken de hele levensperiode tot 6 maanden ná het 1e konsult

7. Is onderstaand ziektebeeld(en) aanwezig en/of maakt deze deel uit van voorgeschiedenis?

nr.	ziektebeeld	nr.	ziektebeeld	-----> vervolg vasculitis	
01 =	lactase deficiëntie	15 =	diabetes type II	Dermatomyositis	Polymyalgia rheumatica
02 =	lactose intolerantie	16 =	chron. obstr. longziekte	Essentiële cryoglobulinemie	Polymyositis
03 =	diverticulitis	17 =	TBC	Familiaire granulomateuze vasculitis	Recidiverende polychondritis
04 =	diverticulose	18 =	M. Graves	Gedissemineerde necrotiseerde periarteritis	Reumatoïde vasculitis
05 =	coeliakie	19 =	hypothyroïdie	Hypocomplementaire vasculitis	Reus cel arteritis
06 =	cholelithiasis	20 =	hyperthyroïdie	Immunoblastische lymfadenopathie	Syndroom van Goodpasture
07 =	pancreatitis	21 =	vasculitis (excl. 10, 11, 12)	Kawasaki syndroom	Syndroom van Moschowitz
08 =	myocardinfarct	22 =	overig	MCTD	Systeemsclerose (sclerodermie)
09 =	CVA			Microscopische polyarteritis	Trombotische -
10 =	SLE			Necrotiserende angitis	trombocytopenische purpura
11 =	pleuropéricarditis			Panarteritis nodosa	Wegener's granulomatosis
12 =	Henoch Schönlein			Periarteritis nodosa	Ziekte van Takayasu
13 =	nefrolithiasis			Polyarteritis nodosa	Ziekte van Sjögren
14 =	diabetes type I			Polymorfie reticulose	

- 1 ☐ nee
 2 ☐ ja $\longrightarrow$
nr.	diagnosedatum (mmjj)	nr.	diagnosedatum (mmjj)	nr.	diagnosedatum (mmjj)
	____		____		____
	____		____		____
	____		____		____
- 9 ☐ onbekend

8. Is er appendectomie verricht?

- 1 ☐ nee
 2 ☐ ja $\rightarrow$ Operatiedatum (ddmmjj)
 $\rightarrow$ Bevinding(en) (maximaal 2)

1 = normaal	5 = lymfadenitis
2 = appendicitis	6 = overig
3 = granuloom	9 = onbekend
4 = passend bij Crohn	

- 9 ☐ onbekend

9. Is er maligniteit van het maagdarmkanaal vastgesteld?

1 ☐ nee

2 ☐ ja ->

nr.	lokatie	nr.	lokatie
05 =	jejunum	13 =	rectum
06 =	ileum (excl. term. ileum)	14 =	anus
07 =	term. ileum	15 =	rectosigmoid
08 =	coecum	16 =	appendix
09 =	colon ascendens	17 =	flexura hepatica
10 =	colon transversum	18 =	flexura lienalis
11 =	colon descendens	19 =	colon NNO
12 =	sigmoid	20 =	overig

nr.	Morfologie
01 =	adenocarcinoom, wel stijmvormend
02 =	adenocarcinoom, niet stijmvormend
03 =	adenocarcinoom NNO
04 =	plaveiselcelcarcinoom
05 =	gemengde adeno-plaveiselcelcarcinoom
06 =	maligne tumoren NNO

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
lokatie	morfologie	maand	jaar
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
lokatie	morfologie	maand	jaar
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
lokatie	morfologie	maand	jaar

9 ☐ onbekend

10. Maligniteit (niet onder vraag 9 vermeld) met diagnosedatum?

1 ☐ nee

2 ☐ ja -> soort:

topografie morfologie
ICD-O kode ICD-O kode datum (mmjj)

.....	<input type="text"/>	<input type="text"/>	<input type="text"/>
.....	<input type="text"/>	<input type="text"/>	<input type="text"/>
.....	<input type="text"/>	<input type="text"/>	<input type="text"/>

9 ☐ onbekend

LICHAMELIJK ONDERZOEK BIJ EERSTE KONSULT

1. Gewicht: afronden op hele kg

9 ☐ onbekend

Lengte: cm

9 ☐ onbekend

2. Distensie buik?

1 ☐ nee

2 ☐ ja

9 ☐ onbekend

3. Perianale afwijkingen?

1 ☐ nee

2 ☐ ja ->

- 1 ☐ fistel
2 ☐ stenose
3 ☐ ulcus/ulcera
4 ☐ fissuur

- 5 ☐ poliep
6 ☐ haemorroid
7 ☐ tag(s)
8 ☐ abces

9 ☐ onbekend

4. Afwijkingen in de mond?

- 1 ☐ nee
2 ☐ ja -> 1 ☐ aften
 2 ☐ ulcus/ulcera
 3 ☐ glossitis
9 ☐ onbekend

5. Buikpalpatie pijnlijk?

- 1 ☐ nee
2 ☐ ja -> meer antwoorden mogelijk: 1 ☐ diffuus 4 ☐ rechter boven quadrant
 2 ☐ rechter onder quadrant 5 ☐ linker boven quadrant
 3 ☐ linker onder quadrant 6 ☐ centraal
9 ☐ onbekend

6. Palpabele abdominale massa?

- 1 ☐ nee
2 ☐ ja
9 ☐ onbekend

7. Acute buik?

- 1 ☐ nee
2 ☐ ja
9 ☐ onbekend

LABORATORIUM ONDERZOEK

Vragen 1a, 1b en 2 bestrijken de periode van de eerste zes maanden ná het 1e konsult, waarbij de periode iets ruimer mag worden genomen naar de huisartsperiode toe.

1a Bloedbepaling klinisch-chemisch/haematologisch

Hierbij wordt de eerst- en laatst bekende waarde geregistreerd, inclusief de datum. Echter de data zijn niet altijd bekend. Indien in 6 maanden tijd maar éénmaal een betreffend nummer is ingevuld dan wordt de 2e kolom blanco gelaten.

	nr.	bloedbepaling	eerste waarde	datum (mmjj)	laatste waarde	datum
	01	= BSE (mm eerste uur)	_____	_____	_____	_____
#	02	= CRP (U/L)	_____	_____	_____	_____
	03	= Hb (mmol/l)	____,____	_____	____,____	_____
	04	= Ht	____,____	_____	____,____	_____
	05	= trombocyten (G/l)	_____	_____	_____	_____
	06	= kreatine (µmol/l)	_____	_____	_____	_____
#	07	= ureum (mmol)	____,____	_____	____,____	_____
#	08	= cholesterol (mmol/l)	____,____	_____	____,____	_____
	09	= ASAT (U/l)	_____	_____	_____	_____
	10	= ALAT (U/l)	_____	_____	_____	_____
	11	= AF (U/l)	_____	_____	_____	_____
	12	= γG (U/l)	_____	_____	_____	_____
	13	= bilirubine (µmol/l)	____,____,____	_____	____,____,____	_____
	14	= totaal eiwit (g/l)	____,____,____	_____	____,____,____	_____
	15	= albumine (g/l)	____,____,____	_____	____,____,____	_____
#	16	= MCV (fl)	_____	_____	_____	_____
#	17	= ferritine (ng/ml)	_____	_____	_____	_____
	18	= FE (µmol)	_____	_____	_____	_____

= de gemerkte bloedbepalingen worden niet geregistreerd bij patiënten die reeds vóór 1 oktober 1991 bij IBD gediagnostiseerd waren

1b Bloedbepaling serologisch

nr.	bloedbepaling	uitslag	datum (mmjj)
1	= yersinia	☐	☐ ☐ ☐ ☐
2	= clostridium	☐	☐ ☐ ☐ ☐
3	= salmonella (Widal)	☐	☐ ☐ ☐ ☐
4	= entamoeba histolyca	☐	☐ ☐ ☐ ☐
5	= overig	☐	☐ ☐ ☐ ☐

uitslag

X = niet getest/geen onderzoek verricht
1 = positief
2 = negatief

Alle uitslagen, ook indien een onderzoek niet is verricht, vermelden. Let op positieve uitslagen, deze zijn zeer belangrijk! Indien op meer dan 3 momenten een faecesmonster is gekweekt, in ieder geval de positieve uitslag vermelden, indien aanwezig. Dit geldt voor vraag 2.

2. Microbiologisch onderzoek

	uitslag	maand	jaar		uitslag	maand	jaar		uitslag	maand	jaar
01 = salmonella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	04 = yersinia	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	07 = cysten	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
02 = shigella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	05 = clostridium	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	08 = candida	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
03 = campylobacter	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	06 = wormeieren	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	09 = tbc	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
								10 = overig	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
01 = salmonella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	04 = yersinia	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	07 = cysten	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
02 = shigella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	05 = clostridium	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	08 = candida	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
03 = campylobacter	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	06 = wormeieren	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	09 = tbc	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
								10 = overig	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
01 = salmonella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	04 = yersinia	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	07 = cysten	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
02 = shigella	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	05 = clostridium	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	08 = candida	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
03 = campylobacter	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	06 = wormeieren	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	09 = tbc	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
								10 = overig	☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

3. Deze vraag is vervallen.

Vragen 1 tot en met 3 bestrijken het eerste half jaar ná het 1e konsult

nr.	onderzoek	nr.	onderzoek
01	Endoscopie	12	Radiodiagnostiek
02	= proctoscopie	13	= X-colonoscop *
03	= sterke rektoscopie *	14	= X-dunne darm
04	= sigmoidoscopie *	15	= echografie
05	= colonoscopie *	16	= CT-scan *
06	= duodenoscopie	16	= MRI *
07	= ileoscopie *		Histologie
08	= jejunoscopie *	21	= biopsi organeel
09	= ileocolonoscopie *	22	= biopsi gerevisiseerd
10	= indium scan *	23	= resectiepreparaat *
		*	= hierbij K/S vermelden

bevindingen per lokatie

blanko	=	niet onderzocht
n	=	normaal
?	=	niet geregistreerd
	=	zie handboek

K/S		
1	II	kontinu
2	III	segmentaal
3	IV	niet bekend
blanko	V	niet van toepassing

											02													13
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								
dag	maand	jaar	onderzoek	k/s	slokdarm	maag	duodenum	jejunum	ileum	term. ileum	coecum	colon asc.	col. transv.	col. desc.	sigmoid	rectum								

-- 02 ----->bevindingen per lokatie <----- 13

Aantal extra ingevulde bladen 1__1__1

2. Lokalisatie ontsteking?

Interpretatie na alle onderzoeken over het laatste half jaar van registratie

Bevinding per lokatie
 blanko = niet onderzocht
 n = normaal
 a = abnormaal
 9 = onduidelijk

*K/S 1 ☐ kontinu 2 ☐ segmentaal

☐ mond ☐ slok- ☐ maag ☐ duode- ☐ jejunum ☐ ileum ☐ term. ☐ coecum ☐ colon ☐ colon ☐ colon ☐ sigmoid ☐ rectum ☐ anus
 darm num ileum (excl term. ileum) ileum ascen- trans- descen- dens

3. Welke diagnose werd door ondergenoemde personen gesteld?

01 = zeker Colitis Ulcerosa 06 = Aspecifieke (onbepaalde) Colitis
 02 = waarschijnlijk Colitis Ulcerosa 07 = onduidelijk
 03 = Chronische Proctitis 08 = normaal
 04 = zeker Morbus Crohn 09 = overig
 05 = waarschijnlijk Morbus Crohn 99 = niet ingevuld

Endoscopist ☐

Radioloog ☐

Patholoog ☐

EXTRAINTESTINALE BEVINDINGEN

Vragen 1 en 2 bestrijken de hele levensperiode tot 6 maanden ná het 1e konsult

1a Hepatobilaire diagnostiek verricht?

1 ☐ nee

2 ☐ ja ->

nr.	diagnostiek	diagnostiek	datum (mmjj)
01	= echografie lever	☐	☐
02	= ERCP	☐	☐
03	= transhepatische cholangiografie	☐	☐
04	= leverbiopsie	☐	☐
05	= overig	☐	☐

9 ☐ onbekend

1b Hepatobilaire afwijking(en)?

nr.	bevinding		
01 =	pericholangitis	08 =	amyloïdose
02 =	prim. scleros cholangitis	09 =	granulomateuze hepatitis
03 =	postnecr. cirrhose	10 =	steatose
04 =	primair biliaire cirrhose	11 =	andere hepatobilaire afwijkingen
05 =	galgangcarcinoom	14 =	onduidelijk
06 =	autoimmuun vorm CAH	15 =	overig
07 =	postinfektieuz vorm CAH		

1 ☐ nee

2 ☐ ja -> bevinding datum (mmjj) bevinding datum (mmjj)

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9 ☐ onbekend

2. Zijn er andere bevindingen met diagnosedatum?

nr.	gewrichtsafwijking	nr.	huidafwijking	nr.	oogafwijking	nr.	vasculaire thromboëmbolie
01 =	M. Bechterew	10 =	erythema nodosum	20 =	conjunctivitis	30 =	diepe veneuze thrombose perifeer
02 =	sacroïlitis	11 =	pyoderma gangrenosum	21 =	uveïtis anterior	31 =	pulmonale embolie/thrombose
03 =	perifere arthralgie	12 =	erythema multiforme	22 =	episcleritis	32 =	cerebrale thrombose
04 =	perifere arthritis	13 =	psoriasis	23 =	scleritis	33 =	a. retinalis thrombose
05 =	clubbing vingers/tenen	14 =	oeczem	24 =	iridocyclitis	34 =	a. mesenterica thrombose
06 =	hypertrofische osteoarthropathie	15 =	herpes zoster	25 =	andere oogafwijking	35 =	thromboëmbolieën (andere lokatie)
07 =	andere gewrichtsafw.	16 =	niet gespecificeerd			36 =	thromboëmbolieën (onbek. lokatie) *
		17 =	andere huidafwijking			37 =	recidiverende thromboëmbolieën (onbekende lokatie) *
						38 =	andere vasculaire thromboëmbolie
						*	geen datum vermelden

1 ☐ nee

2 ☐ ja -> nr. datum (mmjj) nr. datum (mmjj) nr. datum (mmjj) nr. datum (mmjj)

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9 ☐ onbekend

MEDIKAMENTEuze- EN VOEDINGSTHERAPIE

1. Toegediende medicijnen voor IBD:

nr. medicatie	08 = cyclosporine	18 = andere corticosteroiden
00 = geen medicatie	09 = methotrexaat	20 = onbekend welke medicatie
01 = salazosulfapyridine	10 = 1 - 20 mgr prednis(ol)on	21 = onbekend of medicatie
5-ASA	Corticosteroiden	22 = 5-ASA; onbekend
02 = dipentum ®	11 = 21 - 40 mgr prednis(ol)on	23 = prednis(ol)on, onbekend welke dos.
03 = salofalk ®	12 = ≥ 41 mgr prednis(ol)on	24 = onbekend preparaat
04 = peniasa ®	13 = hydrocortison	25 = overige
05 = acosal ®	14 = ACTH	26 = Budesofalk ®
Overige	15 = beclomethason	27 = Budesonide
06 = flagyl ®	16 = Budesonide (Entocort)®	XX = placebo
07 = imuran ®	17 = Rectovalone ®	ZZ = patiënt in dubbelblinde-trial

Toedieningsvorm/route
1 = oraal
2 = klisma
3 = suppositoria
4 = intraveneus
5 = intranasaal
6 = intramusculair

Data
nog = medicatie loopt nog
al = medicatie loopt al
9 = onbekend

nr.	medicatie	toedieningsvorm	begin datum (ddmmjj)	einddatum (ddmmjj)	nr.	medicatie	toedieningsvorm	begin datum (ddmmjj)	einddatum (ddmmjj)
01					21				
02					22				
03					23				
04					24				
05					25				
06					26				
07					27				
08					28				
09					29				
10					30				
11					31				
12					32				
13					33				
14					34				
15					35				
16					36				
17					37				
18					38				
19					39				
20					40				

Aantal extra ingevulde bladen

2. Werd de medikatie voor IBD als gevolg van bijwerkingen (tijdelijk) gestaakt?

- 20 ja-

- 9 ☐ onbekend

Geef hieronder aan om welk volgnummer (1 t/m 40; zie vorige vraag) en welke bijwerking het gaat:

Bijwerkingen

01 = misselijkheid	07 = pancreatitis	13 = eczeem	19 = infertiliteit
02 = braken	08 = nierfunctiestoornissen	14 = rash	20 = spierpijn
03 = diarree	09 = anemie	15 = artritis	24 = overig
04 = anorexie	10 = leucopenie	16 = lymfoom	
05 = buikpijn	11 = trombopenie	17 = hoofdpijn	
06 = leverbeschadiging	12 = paronychie	18 = pleuritis	

volgnr

[illegible]

3. Werd medikatie voorgeschreven (of gebruikt), niet onder vraag 1 vermeld, in de eerste 6 maanden ná het 1e konsult?

- 2
-
- ja -

- 9 ☐ onb

- **End of the world**

Soort medikatie Meer antwoorden mogelijk (voor uitgebreide beschrijving zie hieronder):

- 1 ☐ Acetosal en andere salicylaten

- 2 ☐ overige NSAID preparaten

- 3 orale anticoagulantia

- 4 ☐ maagzuurremmers

- 5 ☐ cholestyramine

- 6 overig

[illegible]

4. Voedingstherapie voor IBD?

1 ☐ nee

2 ☐ ja →

Voedingstherapie:

1= totale parenterale voeding (TPN): intraveneuze voeding

2= perifere parenterale voeding (PPN): intraveneuze voeding

3= elementair dieet: enterale voeding via sonde danwel oraal toegediend

4= sondevoeding (polymeer): enterale voeding via sonde danwel oraal toegediend
Nutrison, Pre-Nutrison, Nutrison-soja, Nutridip, Osmolite, Sondalis ISO, Ensure plus, Renolin, Precitene, Survimed, Pulmocare, Ompact

5= sondevoeding (monomeer): enterale voeding via sonde danwel oraal toegediend
Flexical, Nutri-2000, Peptamen, Pepti-2000 (variant), Peptison, Reabilan, Vivonex

6= sondevoeding (onbekend welk type)

9 ☐ onbekend

nr. begindatum (ddmmjj) einddatum (ddmmjj)

nr. begindatum (ddmmjj) einddatum (ddmmjj)

Indien de patiënt al/nog een voedingstherapie heeft, dan alleen begindatum vermelden en bij de einddatum 9's invullen.

1. Darmresektie?

- 1 ☐ nee
2 ☐ ja _____
9 ☐ onbekend

- 1 = falen conservatieve therapie
- 2 = stenose/strictuur
- 3 = perforatie
- 4 = toxisch megacolon
- 5 = fistel
- 6 = abces
- 7 = infiltraat
- 8 = acute buik
- 9 = overig

nr.	lokatie	nr.	lokatie
01 =	mond	09 =	colon ascendens
02 =	slokdarm	10 =	colon transversum
03 =	maag	11 =	colon descendens
04 =	duodenum	12 =	sigmoid
05 =	jejunum	13 =	rectum
06 =	ileum (excl. term. ileum)	14 =	anus
07 =	term. ileum	15 =	overig
08 =	coccyum		

Restlengte is alleen van belang bij resecties, d.w.z. lokaties 04 t/m 07. Bij andere lokatiecodes niets vermelden.

lokatie	datum (ddmmjj)	lengte resekite dunne darm (cm)	rektalengte dunne darm (cm)	redenen
lokatie	datum (ddmmjj)	lengte resekite dunne darm (cm)	rektalengte dunne darm (cm)	redenen
lokatie	datum (ddmmjj)	lengte resekite dunne darm (cm)	rektalengte dunne darm (cm)	redenen
lokatie	datum (ddmmjj)	lengte resekite dunne darm (cm)	rektalengte dunne darm (cm)	redenen
lokatie	datum (ddmmjj)	lengte resekite dunne darm (cm)	rektalengte dunne darm (cm)	redenen

2. Darmanastomose?

- 1 ☐ nee
2 ☐ ja →

- nr.
- 01 = proctocolectomy met Brooke ileostoma;
Verwijdering van colon, rectum en anus, waarna
ileum door een incisie van de abdominale wand
wordt gehaald (zo'n 5 cm buiten buikholte) en
vervolgens aan de buikwand wordt gehecht. Dit is
een zogenaamd eindstandig ileostoma, waarbij geen
continentie wordt verkregen.
- 02 = proctocolectomy met continent ileostoma (Kock pouch);
Verwijdering van colon, rectum en anus, waarna een
S-vormig reservoir wordt gemaakt van het terminale
ileum, dat vervolgens aan de buikwand wordt
vastgehecht. door intubatie van de pouch, drie maal
per dag, wordt drainage van de faeces verkregen.
- 03 = partiële colectomie met ileorectale anastomose (IRA);
Verwijdering van het colon minus het rectum,
waarbij het ileum end to end op het rectum wordt
geplaatst. Continent
- 04 = partiële colectomie met anastomose ileum/ander colon deel;
Verwijdering van een deel van het colon met end to
end vasthechting van ileum aan resterende colon.
Continent.
- 05 = ileoanale anastomose "end to end";
- 06 = ileoanale anastomose (Parks pouch) met J-loop reservoir;
- 07 = ileoanale anastomose (Parks pouch) met S-loop reservoir;
Verwijdering van het colon en rectum waarna end to
end verbinding met anus, zonder (05), met J-vormig
(06) of met S-vormig reservoir (07)
- 08 = ileoanale anastomose (Parks pouch) met W-loop reservoir;
- 09 = loop ileostomie;
Dit wordt gebruikt voor tijdelijke decompressie van
het colon. Een lis van het ileum wordt naar buiten
gebracht en in de buikwand gehecht
- 10 = splitileostomie;
Aan- en afvoerende lis van het ileum worden apart
op de buikwand gehecht. Dit wordt eveneens
gebruikt voor decompressie van het colon
- 11 = opheffen Hartman/colorectale anastomose
- 12 = overig

9 ☐ onbekend

nr.	dag	maand	jaar
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
nr.	dag	maand	jaar
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
nr.	dag	maand	jaar
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

3. Bevindingen mogelijk gerelateerd aan operatieve ingrepen darmresectie en darmanastomose:

nr.	bevinding	03 =	fistelvorming	05 =	short bowel	07 =	adhaesies	09 =	peritonitis
01 =	pouchitis	04 =	recidief naad	06 =	diversion colitis	08 =	abces	10 =	overig
02 =	dunne darm obstructie								

bevinding datum vaststelling (ddmmjj)

bevinding datum vaststelling (ddmmjj)

bevinding datum vaststelling (ddmmjj)

4. Fisteloperatie en verbinding?

- 1 ☐ nee
2 ☐ ja →
9 ☐ onbekend

nr.	lokatie	nr.	lokatie
01 =	mond	09 =	colon ascendens
02 =	slokdarm	10 =	colon transversum
03 =	maag	11 =	colon descendens
04 =	duodenum	12 =	sigmoid
05 =	jejunum	13 =	rectum
06 =	ileum (excl. term. ileum)	14 =	anus
07 =	term. ileum	15 =	overig
08 =	coecum		

verbinding	
01	= blinde fistel
02	= twee darmdelen
03	= darm en blaas
04	= darm en vagina
05	= darm en huid
06	= darm en buiholte
07	= darm en urethra
08	= verbinding onbekend
09	= overig

lokatie

lokatie

dag maand jaar

dag maand jaar

verbinding

verbinding

5. Overige operaties van het maagdarmkanaal in verband met IBD?

- 1 ☐ nee
2 ☐ ja →
9 ☐ onbekend

nr. dag maand jaar nr. dag maand jaar nr. dag maand jaar

01 =	exploratief
02 =	stricturoplastiek
03 =	abces
04 =	overig

6. Macroscopisch aspect van de darm volgens de operateur?

01 = ziekte van Crohn of transmurale ontsteking
02 = colitis ulcerosa of niet transmurale ontsteking
03 = onduidelijk

04 = overig
05 = niet vermeld

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
nr.	dag	maand	jaar	nr.	dag	maand	jaar

KONKLUSIE (invullen door panel)

1. Wat is de diagnose van onderzoeker volgens de criteria van het IBD project?

01 ☐ zeker Colitis Ulcerosa	09 ☐ microscopische colitis
02 ☐ waarschijnlijk Colitis Ulcerosa	10 ☐ lymfogene colitis
03 ☐ Chronische Proctitis	11 ☐ pseudomembraneuze colitis
04 ☐ zeker Morbus Crohn	12 ☐ bestralingsenterocolitis
05 ☐ waarschijnlijk Morbus Crohn	13 ☐ ischaemische colitis
06 ☐ aspecifieke (onbepaalde) colitis	14 ☐ infectieuze colitis, te weten
07 ☐ collagene colitis	15 ☐ normaal
08 ☐ eosinofiele colitis	16 ☐ onduidelijk
	17 ☐ overig

Speciale attentie voor de onderzoeker:

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